American Heart Journal

Vol. 27 | January, 1944 | No. 1

Original Communications

AN INTIMATE ACCOUNT OF MY EARLY EXPERIENCE WITH CORONARY THROMBOSIS

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FROM time to time for twenty-five years or more it has been suggested to me that I write a history of the coronary artery and its diseases. Among those who have most strongly urged this have been Dr. Joseph A. Capps of Chicago, Dr. Frank N. Wilson of Ann Arbor, and Dr. Fred M. Smith of Iowa City. On Dec. 18, 1935, a direct personal appeal was made by Dr. Wilson.

In his letter he said that I was chiefly responsible for impressing upon the medical profession the importance of coronary occlusion. He felt that a small book giving "details that never get into the concise reports written for publication in a medical journal . . . would be of great value."

I replied that I had decided not to write the book. It seemed unwise to do what would lead students and practitioners, who in the future might be seeking information on the subject, to depend upon an abstract, even though it was made by the author himself. It was much better for them to consult the original articles. Moreover, it was doubtful whether today I could accurately depict my mental processes of twenty-five years ago; unconsciously, the ideas of later years would creep in. Besides, there would be no freshness about writing such a book; it would be little more than a repetition of what I had already said. At 74 years of age the task would be onerous and irksome. Nor was I as competent as many others to discuss adequately certain features that were involved, e.g., the electrocardiogram and some physiologic principles. His letter had, however, opened up the whole question as to whether I ought to tell the story of how I "got onto" the clinical features of acute coronary occlusion.

Received for publication Nov. 15, 1943.

In a letter of Jan. 3, 1936, Dr. Wilson urged that "an intimate account of your early experiences with coronary thrombosis would be of the greatest interest both to the present and to future generations." It would, he added, have an historical value. It would help to impress the *importance of study of the patient at the bedside*, of using eyes, ears, fingers, and of making and preserving careful records of observations. He commented on the fact that my results had been obtained without the help of new instruments of precision or any new method of examination. An article such as he was advising would, he believed, encourage others to make similar studies.

This matter, while not entirely forgotten in the last seven years, has not been taken up earlier for several reasons: concentration on preparing for, and writing, *A Short History of Cardiology;* a long, serious illness; pressure of many other interests that at the time seemed to call for immediate attention; and the attitude of the octogenarian who hesitates to undertake what, to him, appears to be a formidable task. My decision not to write the larger history of the coronary artery and its diseases has not been changed. There are many of the younger group who, more appropriately and more satisfactorily than I, can write such a volume.

The decision to write in accordance with the suggestion in Dr. Wilson's letter, with the purpose of telling how I became aware of the frequent occurrence of acute coronary occlusion and realized the possibility of its clinical recognition, has been reached for several reasons:

1. The earnest solicitation of three friends, Doctors Capps, Wilson, and Smith, on whose good judgment I place much reliance.

2. The importance of the subject. There is truth in what Roy Scott wrote in 1930: "Medical history of the future doubtless will record as one of the important contributions to the past twenty years, the general recognition of coronary thrombosis."

3. D. E. Bedford's statement (*Practitioner*, June, 1933) that "the knowledge that coronary thrombosis is compatible with life and even health and that it can be recognized with certainty in many cases, has come to us in the last twenty years and we owe it largely to the work of American physicians, and," he adds, "especially to Herrick."

4. The interest that has been manifested when I have talked casually of it to friends, and especially that which was shown on two occasions when in an intimate way I spoke to small groups of doctors.

In 1927, in Pasadena, at an impromptu meeting of the "Stanley Black Club" (there were perhaps thirty doctors at the gathering) I told how my curiosity about the subject had been aroused, and recited details of my experience with my first case.

April 12, 1933, I addressed the attending and resident staffs of the Mayo Clinic at Rochester, Minnesota. Particulars of the first three cases with autopsy were gone over. My notes for this off-the-record

talk show that I closed with an expression of the hope that my young hearers would get from it two ideas. The first was that all medicine needs periodic overhauling. We should avoid the paralyzing influence of the dead hand of tradition, should get away from "the habit complex of groove thinking that is so prevalent in medicine."[1] I cited Laubry[2] as saying that the desirability of periodic revision of ideas applied particularly to diseases of the heart. The second lesson was, though some leaders did not agree, that there was still room for sane, careful, bedside observation. Neither the all-time hospital clinician nor the laboratory worker had a just claim to proprietary ownership of productive, healthy doubt and skepticism. There was a place for all types of investigation. The laboratory, the ward, the library should all be regarded as workshops for observation, experiment, and logical thinking. The watchword should be cooperation. Will Mayo told me later that I would never know how much good that talk had done his staff in the way of stimulation and encouragement.

5. In reviews of my *Short History of Cardiology* there are expressions of regret that, while several pages are devoted to an historical résumé showing how coronary thrombosis (a topic to which "the author himself had made many worthy contributions") was for long overlooked, the subject of how it was "put on the map" has not been taken up. When such men as Sir Thomas Lewis, Paul D. White, E. B. Krumbhaar, and the writer of the unsigned review in the London *Lancet*, Feb. 6, 1943, express themselves in this fashion, one must listen seriously and respectfully.

This, then, is my apologia, with that word's triple implication of apology, explanation, and—if necessary—defense, for writing this very intimate and very personal paper.

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A few words regarding the character of my work from the time of my graduation from Rush, in 1888, to 1912, the date of my first paper on "Coronary Occlusion," seem to be in order. At the close of my internship in Cook County Hospital, in 1889, I knew that I was not cut out for a surgeon, nor for an obstetrician or gynecologist. Though ophthalmology, dermatology, and neurology held out attractions, my leanings were definitely towards internal medicine. For at least twenty-five years my aim was to be an all-round practitioner, an internist, as one often says nowadays. In the last two decades, much against my will, there has been forced upon me the term "heart specialist."

Yet, in retrospect, I see that even from student and intern days heart disease attracted me. There still remains the memory of my excitement over my first case of angina pectoris. The patient was a simple, intelligent German, whose story of attacks of pain sounded like angina and yet left me hesitating to venture such a diagnosis un-

til, one day as I was making ward rounds, I saw him sitting erect in a chair, pale, the picture of anguish. At my order the nurse rushed for the nitrite of amyl. After a few inhalations, a look of incredulity came over him. As, breathing more freely, he relaxed from his tense attitude, tears came into his eyes, and, with the courtesy of the old-world peasant, he grasped my hand and kissed it. I was almost as incredulous as he; it was too good, too marvelous, to be true.

Then, probably because I early taught physical diagnosis, I became enamored of heart murmurs and other signs of heart disease. There was perhaps a little playing to the gallery of students and interns when one made a diagnosis of mitral stenosis by simple palpation that revealed the presystolic thrill and the sharp pulmonic valve closure; or when, by noting the collapsing or capillary pulse, or the Duroziez phenomena, one recognized aortic regurgitation. At that period I was often called to see a supposed case of typhoid fever, which disease was then prevalent in Chicago. There was real pleasure in demonstrating to the attending doctor that his patient was suffering, not from typhoid, but from a malignant type of endocarditis; in explaining that he should view the condition, not from the standpoint of the mechanics of the valve, but of an infection. The valve was not only a freshly infected, but was an actively infecting, focus.

It is clear to me now that my attitude toward diagnosis in general had much to do with my early recognition of coronary thrombosis. Diagnosis appealed to me very early, even in intern days. An obscure case was a challenge to one's keenness of observation and skill in interpretation. There was a feeling of satisfaction if a diagnosis was shown to be correct; one of disappointment if it was wrong. Chagrin at failure might be tempered by finding that the condition was one that was practically impossible of intra-vitam recognition, or one that was irremediable by drug or surgery, e.g., an inoperable carcinoma. Chagrin was changed to bitter remorse if it was revealed that, through delay in diagnosis, or because of a wrong diagnosis, the opportunity for proper treatment had been lost and a life sacrificed, e.g., as in perforation of the bowel in typhoid fever.

Another proof that, by 1910, I had been a good deal occupied with heart disease is that I had already written several papers about it: "Tricuspid Stenosis" (1897), "Concretio Cordis" (1898), "Healing of Ulcerative Endocarditis" (1902), "Erroneous Notions Concerning Angina Pectoris" (1910). When, therefore, the first case that I recognized as acute coronary occlusion came along, I was pretty familiar with the literature of heart disease and had had quite an extensive clinical experience with it. Moreover, and this seems to me an important feature, I had as a background a knowledge of general medicine. I felt at home in the field of diseases of the lung, stomach, bowel, and kidney; had seen many cases of diabetes, exophthalmic goiter, diseases of the blood,

and infectious diseases; and I had taught these subjects to students, both didactically and clinically. The wise pathologist, when he looks at a stained section for microscopic diagnosis, before turning on the oil immersion lens, uses first the low power. Or he may even do as did Hans Chiari, under whom, in 1894, I studied in Prague: always hold the slide up to the light, and look at it first with the naked eye. The wider field of vision enables him to understand more clearly the relation of parts, an important factor in trying to reach a diagnosis. So, when confronted by a puzzling case, it had become almost second nature to me, after the analogy of the pathologist, first to consider the case in its broader relations, and to think of the heart only after disease in other organs had been with reasonable probability excluded; it was illogical and often disastrous to jump hastily to the conclusion that the heart was at fault.

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The history of my first case of acute coronary occlusion is copied, with a few minor changes, from my article, as read before the Association of American Physicians, May 14, 1912.[3]

Case 1.—*History.*—On Jan. 16, 1910, a man, aged 55 years, supposedly in good health, was seized an hour after a moderately full midnight meal with severe pain in the lower precordial region. He was nauseated, and, believing that something he had just eaten had disagreed with him, he induced vomiting by tickling his throat. The pain continued, however, and his physician was called. He found him cold, nauseated, with small, rapid pulse, and suffering extreme pain. The stomach was washed out and morphine given hypodermically. The pain did not cease until three hours had passed. From this time on, the patient remained in bed, free from pain, but the pulse continued rapid and small, and numerous râles appeared in the chest. When I saw him twelve hours after the painful attack, his mind was clear and calm; moderate cyanosis and mild dyspnea were present. The chest was full of fine and coarse moist râles; there was a running, feeble pulse of 140. The heart tones were very faint and there was a most startling and confusing hyperresonance over the chest, the area of heart dullness being entirely obscured. The abdomen was tympanitic. The urine was scanty, of high specific gravity, and contained a small amount of albumin and a few casts. The temperature was subnormal, later going to 99° F. Occasionally there was nausea, and twice a sudden projectile vomiting of considerable fluid material. This condition remained with slight variations up to the time of his sudden death, fifty-two hours after the onset of the pain, though at one time the râles seemed nearly to have disappeared. A few hours before death the patient described a slight pain in the heart region, but said it did not amount to much. A remarkable circumstance, and one that occasioned surprise in those who saw the patient and who realized from the almost imperceptible pulse and the feeble heart tones how weak the heart must be, was the fact that he frequently indulged in active muscular effort without evident harm. He rolled vigorously from side to side in the bed, sat suddenly bolt upright, or reached out to take things from the table near by; once, feeling a sudden nausea, he jumped out of bed, dodged the nurse, and ran into the

bathroom, where he vomited; and yet he seemed none the worse for these exertions.

Necropsy (Dr. L. Hektoen).—The heart was of normal size. Both coronary arteries were markedly sclerotic, with calcareous districts and narrowing of the lumen. A short distance from its origin the left coronary artery was completely obliterated by a red thrombus that had formed at a point of great narrowing. The wall of the left ventricle showed well-marked areas of yellowish and reddish softening, especially extensive in the interventricular septum. At the very apex the muscle was decidedly softer than elsewhere. The beginning of the aorta showed a few yellowish spots, these areas becoming less marked as the descending part was reached. An acute fibrinous pericardial deposit, which showed no bacteria in smears, was found over the left ventricle. (The pericarditis perhaps explains the slighter pain complained of a few hours before death.) There was marked edema of the lungs. In other respects the anatomic findings were those of health.

A few details are added. The patient was a slender, active man, head of a private banking house. He had taken the midnight meal of a sandwich and a bottle of beer after he and his wife had returned from the theater, in Chicago, to the suburb in which he lived. Twelve hours later, his physician, Dr. L. W. Bremmerman, asked me to see the patient with him. The nature of the persistently rapid, feeble pulse was a puzzling and alarming feature to both of us. We asked help of Dr. Frank Billings. He admitted he did not know the exact cause, but spoke of the possibility of a cardiac accident, such as acute dilatation of the heart. That the accident might be primarily abdominal was considered, and to help rule out some such condition that might call for surgical interference we decided to call in Dr. John B. Murphy.

Dr. Murphy, an intimate friend of the family, quickly responded, and met Dr. Bremmerman and myself. Dr. Billings was not present on this occasion. Dr. Murphy believed that there was no subdiaphragmatic accident, but was much impressed by the hyperresonance of the thorax. Could it be an acute pneumothorax? I felt not, because the resonance was bilateral, râles and breath sounds could be heard on both sides, and, as near as one could make out, there was no dislocation of the heart. The dyspnea was less than one would expect if there were an overwhelming pneumothorax. So threatening was the condition that we called up a son in New York, telling him to hurry home. I shall never forget Dr. Murphy's emphatic way, as, in his rasping voice, he shouted (the long distance connection with New York was not as perfect in those days as now): "No! no! don't wait for the Century tomorrow. Go straight to Mr. ———" (a high New York Central official) "and get a special. What's the matter with you? Get busy, come right away or you'll be too late!"

At the request of the family, Dr. Murphy and I came back in the evening and stayed all night. We were in a big room with twin beds. Murphy, hearing me turn in bed, but not wishing to waken me if I

were asleep, would whisper, "Herrick, are you awake? Say, are you sure about there being no pneumothorax?" A little later, from my bed, also in a stage whisper: "Dr. Murphy, do you think this might be an acute pancreatitis, or possibly a strangulated diaphragmatic hernia?" Neither of us slept much. We got up once or twice during the night to look at the patient.

As recorded in the history, the patient, with little suffering and with little change in condition, lived until about 4 A.M., January 18, when suddenly the heart and breathing stopped. The autopsy by Dr. Hektoen was performed the same day. I was unable to be present. Dr. Hektoen asked me over the telephone what he might expect to find. My reply was, "Look for a clot in the coronary artery. If you don't find that, find a perforated gallbladder or a perforating duodenal ulcer, hemorrhagic pancreatitis, hemorrhage into the adrenals, strangulated hernia, perhaps a diaphragmatic hernia, ruptured pleura, or any other accident you know about." Dr. Hektoen, with the dry humor for which he is well known, with mock courtesy thanked me for giving him such a great variety to choose from. He called me up that evening and said: "The clot was in the coronary artery, all right. But how in God's name did you guess it?" Perhaps guess was the right word. Among my treasured letters is one from Dr. Murphy, who warmly congratulated me on my diagnosis.

As, after more than thirty years, I try to recall the incident, I believe that my ante-mortem diagnosis was reached largely because, in a hurried search for relevant cases, chiefly in textbooks that were in my home library, I was greatly impressed by the case of Panum, which was described by Fraentzel. Panum, after a severe, angina-like attack, had lived fourteen hours. The rapid, feeble pulse had been a striking feature. Autopsy had revealed acute coronary thrombosis. As positive evidence this carried great weight with me because of the similarity of symptoms. On the negative side it seemed justifiable in our case to exclude extracardiac causes for the severe prolonged epigastric pain that had been followed by cardiovascular failure and death. Disease of the gallbladder or perforation of a peptic ulcer seemed unlikely. Rarer conditions, like adrenal hemorrhage, hemorrhagic pancreatitis, and strangulated diaphragmatic hernia were possible, though improbable. While there was no evidence of valvular disease or of enlargement of the heart, and while there was no reason to suspect physical overstrain, the heart seemed to be incriminated. The outstanding feature appeared to be a sudden weakening of the myocardium. Perhaps, after the analogy of thrombosis in cerebral arteries, there had been a thrombotic occlusion of the coronary artery, the nutrient vessel of the heart's muscle.

As, in retrospect, I go over the whole incident again, and try to reconstruct my mental state and the processes of reasoning I went through at that time, I realize that the interpretation appears far simpler after the event than it was in those two hectic days, in which there were many

doubts, many shifts of opinion, many hours of genuinely anxious uncertainty. The old adage about the superiority of hindsight over foresight may well be applied in this instance.

That I did not at once grasp the full significance of the first case is evident from the rather casual reference to it contained in a paper[4] that I read in June, 1910, in the Section on Practice of Medicine of the American Medical Association at the meeting in St. Louis. I said that, in some of the most serious cases of angina pectoris, "there is low blood pressure, indicating perhaps a weakened myocardium. In a man 54 years of age [*sic*] with no general arteriosclerosis, I have seen the rough-walled left coronary plugged in its anterior branch with a thrombus producing sudden excruciating precordial pain. For the fifty hours that the patient lived the heart tones were barely perceptible, and the peripheral pressure extremely low. But in cases in which there is no such acute and extensive myomalacia cordis as was present in this instance, the pressure may be low for a long time and the patient busy about his work, though interrupted at times by the attacks" (of angina pectoris).

Soon after this, however, evidently from further reading and study, I realized more clearly that cases of this type were not rare and that the whole subject was worth more extended observation. This is shown by the fact that in October, 1910, I had seen in consultation a man 65 years of age who had lived seven days from the onset of what, from the typical symptoms, was to my mind an unquestioned case of coronary thrombosis in one who had for some three years been a sufferer from angina of effort. This is recorded as Case 2 in my paper of 1912.

It is evident that, long before May, 1912, when I read my paper at the Association of American Physicians, I had become much surer of my ground, for, in May, 1911, at Des Moines, in the course of an address on "Pain in Disease of the Heart," delivered before the Section on Medicine of the Iowa State Medical Society, I devoted about 1,500 words to acute obstruction of the coronary artery.[5] The views there expressed were based on the first case with autopsy (1910), and five others without autopsy. The views, and largely the language, are those contained in the later paper of May 14, 1912. The concluding paragraph is perhaps worth quoting, as it shows that my ideas at that time were pretty well crystallized, and because it voices the same notions regarding the possibilities and value of noninstrumental diagnosis that are referred to by Frank Wilson in his letter of Jan. 3, 1936. With slight alteration in punctuation and the construction of a sentence, it closed as follows:

"This address, if it accomplishes its aim, will encourage the specialist and the research worker to go forward with the use of the newer instruments and with the investigations by which new facts concerning the heart will come to light. It will also, I trust, encourage the general practitioner to retain some of his old self-confidence and not to lose

faith in his powers of observation and in his ability to analyze subjective symptoms; and still to believe that it is possible by well-established methods of physical diagnosis to understand many of the anatomic, pathologic, and physiologic conditions of this important organ.''

Finally, the decision was reached that, after a more thorough study, I would report the case in a special paper. Far-reaching lessons might be drawn from it. A condition previously regarded as merely a pathologic curiosity had been met with in a man who had lived fifty-two hours. In that time symptoms had developed. Might not other similar cases be discovered in the literature, and enough common features be found to enable a clinical picture to be drawn that would make an intravitam diagnosis possible? Moreover, if Panum had lived fourteen hours and my patient fifty-two, might not others live longer? The more I read on the subject and pondered over it, the clearer it became to me that sudden death was by no means the inevitable sequel to the accident. One could find numerous examples in the literature. George Dock, as early as 1896, had recognized and described such cases. Osler had been aware that in some instances of angina pectoris there were thrombotic lesions in the coronary arteries. Obrastzow and Straschesko, though inclined to regard the accident as ushering in an ultimately fatal status anginosus, had, in 1910, drawn a remarkably accurate clinical picture of the condition. If one read between the lines, one could interpret some of Huchard's and Mackenzie's cases as examples of coronary occlusion. And there were others. I gradually became convinced, quoting from my paper of May, 1912, that ''one may conclude, therefore, from a consideration of the clinical histories of numerous cases in which there has been careful autopsy control, from animal experiments and from anatomic study, that there is no inherent reason why the stoppage of a large branch of a coronary artery, or even of a main trunk, must of necessity cause sudden death. Rather may it be concluded that while sudden death often does occur, yet at times it is postponed for several hours or even days, and in some instances a complete, i.e., functionally complete, recovery ensues.'' It was reasonable to assume, also, that milder cases might be met with. So, on the basis of clinical symptoms, I made a tentative grouping that is recorded in my paper and need not be repeated here.

The clinical picture there drawn seems to me, even now, to be fairly accurate. On the whole it contains little that needs deletion or apology; though, if I were to rewrite it today, I would modify my advice as to the use of digitalis as a routine measure in treatment. Many things were overlooked. Since that date countless details have been added by workers in the United States and other countries, and especially since help from the electrocardiograph has been available. No attempt is made here to review these contributions.

One of the strange things about it all, a fact that has caused me regret, is that I overlooked, even in the paper of 1918, so much pertinent material that had been published before. This was partly because of not following more thoroughly certain leads; it was partly because in my reading I was looking for references under the heading "coronary artery." Had I grasped the bibliographic significance of "infarct of the myocardium" I might have unearthed the mine of information contained in René Marie's monograph *L'Infarctus du Myocarde et Ses Conséquences* (1896). To miss the later monograph of M. Sternberg, *Das chronische partielle Herzaneurysma, Anatomie, Klinik, Diagnose* (1914), was a little more excusable though greatly to be regretted. If I remember rightly, it was Joseph T. Wearn, of Cleveland, who, soon after I had read my paper on "Thrombosis of the Coronary Arteries" in 1918, called my attention to these important papers that had escaped my notice.

As is shown in the chapter on the coronary artery, in my *Short History of Cardiology*, the significance of several other writings was not fully realized. Weigert, Huber, Leyden, and others had discussed this condition. I was not the only one, however, who failed to appreciate fully the message contained in their writings; even their fellow countrymen had paid little heed to their words.

It seemed strange to me at the time, it seems strange to me now, that when, in 1912, I read before the Association of American Physicians a paper that seemed to me to contain an important announcement, it fell like a dud. No one, except Emanuel Libman, discussed it or even asked a question. I must have been keyed up to a high pitch, for I recall my eagerness to have the article published promptly; I feared someone else might jump into print ahead of me. My anxiety about priority was groundless. Even after its publication in the *Journal of the American Medical Association*, in December, 1912, it aroused no more comment than it did when it had been read six months before. No really live interest in the topic was manifested until the second paper, on "Thrombosis of the Coronary Arteries," was read before the Association in 1918. This contained reports on two other patients, with the autopsy findings. It contained, besides, a record of Dr. Fred M. Smith's laboratory experiments on dogs, with lantern slides of electrocardiograms and pathologic specimens. In those days, and it is often true today, a lantern slide or a graph, or an experiment on a dog in a laboratory, attracted greater attention than mere observations made at the bedside on human beings.

It is surprising how easy it is, as Isaiah noted long ago (Isaiah 42:20), to hear but not understand, to see but not really observe. We are all human; we have all erred in this respect. At times I wondered why my early paper had attracted no attention; why my Des Moines address had apparently fallen on deaf ears. Then, too, in 1917, at the New

York meeting of the American Medical Association, in the Section on Medicine, I had read a paper on "Angina Pectoris" that had been written by Frank Nuzum and myself.[6] Its reception, when printed, as when read, seemed to me strange. Comments were restricted almost entirely to our statistics and to the more well-known symptoms. That we had described with emphasis the type of angina associated with coronary thrombosis attracted no attention.

By the end of 1910, and especially after 1911, when I read the paper in Des Moines, I began consciously to do what I called missionary work, preaching the gospel of the pathology and clinical symptoms of acute coronary obstruction. In lectures to students, in clinics, in consultations with physicians and in talks before medical societies in Chicago and elsewhere, I talked coronary occlusion almost ad nauseam. A few listened attentively, more, incredulously, the majority, indifferently. I recall an informal talk before a meeting of Western Surgeons in the Rush amphitheater, in which I stressed the resemblance of the accident to acute abdominal surgical conditions. I can still see the quizzical look on Charlie Mayo's face as, from a front seat, he listened to, but was evidently not converted by, my sermon. About a year later, however, a well-known Chicago surgeon called me by telephone and said he had just been asked to go to Iowa to operate on a patient with gallstones. The history of the case, as related to him by the attending doctor, called to mind, he said, something he had heard me refer to in my talk to the surgeons. Had I any reprints of any article on the subject that I could rush to him? I furnished the reprint. Two days later he called me up and said the case in Iowa was a "dead ringer of your coronary thrombosis. You certainly saved one chap from an unnecessary, serious operation."

At times I feared I might be overenthusiastic, too readily "believing to be true that which I wished to be true." I often asked Dr. Smith and my interns, who shared my enthusiasm, whether I was becoming "nutty." They thought not.

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Then, in March, 1914, there came along the second case in which there was an autopsy. This strengthened my belief that the accident was of not infrequent occurrence and that it could be diagnosed. The case is briefly reported in the paper on "Coronary Thrombosis" read in May, 1918.[7]

Case 2.—A man, aged 62 years, while walking on the boardwalk at Atlantic City, was seized with a terribly severe pain in the lower precordia. He was helped to the hotel, but refused to call a physician while in Atlantic City or for the next two days while in New York, for, as he said, he knew from the severity of the initial pain, the great weakness, and difficult breathing that he would be ordered to a hospital, and he wished to get to his home in Chicago for his illness and, as he feared, his death. He lived over two weeks from the onset of the attack, dying

March 22, 1914. His heart when he reached Chicago was dilated, weak, and somewhat rapid. His blood pressure became progressively lower. There were dyspnea, cyanosis, marked edema of the legs, and albuminuria. Death was as in ordinary cardiac failure. Necropsy revealed recent plugging by a thrombus of the descending branch of the left coronary artery, with softening of the heart muscle at the left apex and lower interventricular septum.

This patient was under the care of Dr. Joseph A. Capps, who represented the family physician, Dr. Frank Billings, who was abroad at the time. The patient had been in such distress while on the journey from New York to Chicago that he had asked his friend, Dr. L. L. McArthur, whom he met on the train, to help him. Dr. McArthur, I believe, gave him a hypodermic of morphine and assisted in his care after he reached Chicago. I saw the patient several times with Dr. Capps and Dr. McArthur. The diagnosis of acute coronary occlusion seemed warranted. There was no reason for suspecting preceding heart trouble, as the man shortly before had been carefully examined by Dr. Billings and pronounced in good health, with nothing abnormal as to heart, blood pressure, urine, etc. The sudden knock-out blow, with its prolonged pain, breakdown of heart's function, and with increasing congestive failure in spite of rest and other measures that were employed, made it almost certain that the coronary artery was occluded. So distressing was the dyspnea, so pronounced the venous distention, and so marked the cyanosis, that venesection was deemed advisable and was performed by Dr. McArthur a day or two before the patient died. The autopsy by Dr. Hektoen showed, as in the first case I had seen, that the sclerosis was limited almost entirely to the coronary artery. In the first case, while aortic sclerosis was not marked, there was more than in this second case, and the coronary artery was more involved.*

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It is to be noted that, in the study of the cases reported before 1918, there had been no help from the electrocardiograph. Between 1910 and 1918 a Cambridge instrument was installed in Presbyterian Hospi-

*In a letter dated May 29, 1943, Dr. Capps, in answer to my request for criticism of the first draft of the manuscript of this paper, reminded me that I had failed to refer to the finding of bacteria in the heart of this patient. "You may recall," Dr. Capps writes, "that the patient was suffering from a cold at the time of onset, and that Dr. Hektoen found, in sections of the coronary artery, cocci overlying an atheromatous patch, and described layer after layer of fibrin deposited on the nucleus of bacteria. And," Dr. Capps adds, "you refer to another case of thrombosis in which infection was a factor. I thought this might be a little further emphasized as a causative factor in a certain group of cases."

In my reply I thanked Dr. Capps for so properly calling to mind what I had entirely forgotten. It was true, I agreed, that not infrequently bacteria have been found at necropsy on patients dying of acute coronary thrombosis. It was also true that a time relation between an existing focus of infection and the clinical symptoms of the "heart attack" has often been noted. But I was not thoroughly convinced that in all, or even a majority, of these cases, the coronary lesion was due to infection from such a focus. It is so easy to find a focus when it is being looked for: few persons are without one or two at least. And we should not apply too readily the old, false *post hoc ergo propter hoc* argument. There is the possibility of mere accidental association. Also, the bacteria in the case of this patient might have been due to a complicating or a terminal infection. "Yet, you may be right," I added, "I know that Dick, Irons, and others have been impressed by the view that acute coronary thrombosis is often (some say it is the rule) due to an infectious process that may be in some remote focus: tonsil, teeth, gallbladder, appendix, or bronchi."

tal, Chicago, through the generosity of Madam Cyrus H. McCormick. Through other funds contributed by her and the late Richard T. Crane, Jr., research was made possible. At this time, also, I installed an instrument in my office. Dr. Smith, after some preliminary study of the anatomy of coronary arteries in dog and man, and their anastomoses, began his pioneer experiments in ligating the coronaries in dogs, with electrocardiographic studies. This work, in which he was aided by Dr. Edwin M. Miller who did the preliminary surgical operations, was done in the basement of the Hospital. As the animal cages were kept across the street in the Rush laboratory building, much arduous transfer of animals back and forth to the electrocardiographic room was necessary. The unremitting zeal and enthusiasm of Dr. Smith deserve highest praise. At first I set his problems for him, with suggestions as to technique. I had to hold him down a little. Soon, however, he came to me asking my advice about some new plan. A little later, he came to me not for advice, but to announce what he was going to do or had already done; he had gotten away from me, was ahead of me. His results, largely incorporated in his important paper[8] of 1918, as well as in later articles, are well known to students of heart disease.

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It became evident from Dr. Smith's investigations that a fairly constant change in the electrocardiogram was brought about by ligation of coronary arteries in the dog, so that one could predict with reasonable certainty the alteration that would appear in the tracing after experimental stopping of circulation in particular branches. We were now on the alert to see if we could utilize this knowledge in the case of some human being whose symptoms suggested acute coronary obstruction. Might it be possible to localize a lesion in the coronary system with an accuracy comparable to that with which one locates obstructing lesions in the cerebral arteries?

The long-looked-for patient came into my office May 3, 1917, at which time I happened to be absent from the city. The late Dr. James R. Greer, my office assistant at that time, obtained the history, took an electrocardiogram, and ventured a diagnosis of acute coronary obstruction, in which diagnosis Dr. Smith concurred. On my return to the city a few days later, I joined in the excitement aroused by the incident and agreed with Dr. Greer and Dr. Smith that this diagnosis was correct, because of the history and striking resemblance of the electrocardiogram to some of those in Dr. Smith's dogs.

The patient, a physician, 37 years of age, an ex-intern of our Presbyterian Hospital, who had never suffered from angina pectoris, had no acute or chronic infection so far as he knew, and who regarded himself as free from cardiovascular and renal disease, twenty days before had been seized, while in this seemingly good health, with a sudden, excruciating pain in the lower sternal region, which pain radiated to the

arms and to the epigastrium. He was profoundly shocked, very weak and nauseated, the skin cold and clammy, the pulse rapid and thready. His colleagues who saw him thought he would die in a very short time. Morphine, ¾ grain, was necessary to control the pain. After a time he rallied, and in about fifteen days was able to be about and even tried to do some professional work. But in a few days his weakness, precordial distress on exertion, dyspnea, and irregular, rapid, and small pulse caused him to give up. He rested, again improved, and came to Chicago. Rest and small doses of digitalis were ordered. On May 31, 1917, he returned for a checkup, and the condition seemed better. The summer vacation was spent on an island in Lake Michigan, where there was considerable violation of the injunction as to quiet and digitalis, the patient not only eating very heartily, but not infrequently going on strenuous walks, fishing and hunting trips, even though precordial pain, occasional attacks of dyspnea, and cardiac irregularity gave warning that the heart was far from normal. From an unduly severe strain of this sort he suffered for several days with dyspnea and arrhythmia; he contracted an infectious bronchitis and hastened to Chicago, where, in a deplorable condition, he went under my care in the Presbyterian Hospital, Sept. 26, 1917. The dyspnea and cyanosis were marked; he was sleepless and had Cheyne-Stokes breathing; the temperature rose to 102° F. The blood pressure was not high, the heart was slightly enlarged to the left, and there was a faint systolic murmur at the apex. After four days he developed signs of pneumonia; the respiration rose to 32 and the temperature to 106° F. There were bloody and rusty sputum, marked albuminuria, and leucocytosis. He became delirious, and just as a distinct drop in temperature and a clearing of the mind made one wonder if recovery after all might be a possibility, he died suddenly. Necropsy, on October 8, by Dr. Thatcher, of Presbyterian Hospital, disclosed pneumonia of the lower lobe of the right lung and several infarcts in other portions of the same lung.

The heart weighed 415 grams. The enlargement involved both right and left sides. The external surface was fairly normal in appearance, with the exception of a pale, depressed area 4 cm. in diameter, midway between the base and apex of the left ventricle, and a smaller, similar area on the lateral surface close to the apex. The wall of the left ventricle near the apex and the interventricular septum were thin and of gristly consistency, cutting with marked resistance. The endocardium of the left ventricle had a pale, mottled appearance, especially marked over the lower three-fourths of the septum and the papillary muscles. The papillary muscles were smooth, contracted, and firm, these changes being particularly marked in the anterior muscle. The greater extent of the fibrous changes in the endocardial and subendocardial tissues, as compared with those on the external surface of the heart, was striking. The left coronary artery contained an organized thrombus in the ramus descendens anterior, 3 cm. from its origin. Also, the first descending branch of the circumflex was occluded 1.5 cm. from its origin by a fresher thrombus. The coronary arteries showed sclerotic plaques scattered throughout most of their course, these spots varying in size from 0.5 to 2 mm. in diameter. The aortic leaflets were thickened. There were a few sclerotic areas in the suprasigmoid area of the aorta. These were not regarded as syphilitic. It may be added that no history or stigmata of syphilis were noted during life, and that the Wassermann test on the blood had been negative.

This case made a profound impression on all of us. It seemed to furnish incontestable proof that the thesis we had so long been harping on was correct; that acute coronary thrombotic occlusion was not rare; that patients might live for many days after the accident; that in a large proportion of cases the clinical picture was typical enough to permit an intra-vitam diagnosis. More than that, the electrocardiogram not only aided materially in diagnosis, but offered hope that it might reveal the location of the resulting myocardial damage, and, in a measure, its extent, and thus be helpful in the way of prognosis and treatment. These facts were presented in my paper that was read before the Association of American Physicians in May, 1918. The similarity between the electrocardiograms of Dr. Smith's dogs soon after ligation and that of the patient at his first visit, when he was fairly comfortable and able to be about, was striking. No less striking were the tracings made on dogs thirty-four days after ligation of the ramus circumflexus sinister and that taken of the patient 178 days after his illness, when he was in the deplorable condition during his stay in the Hospital. The low amplitude and the widened QRS curves, with other abnormalities, were startlingly alike. These were shown in my paper, and also in Dr. Smith's article, published in the *Archives of Internal Medicine,* June, 1918.

An interesting episode may be mentioned, as showing the attitude of mind of even excellent men at that time. My patient, the doctor, after his first interview with me, went to make a social and semiprofessional visit on a prominent colleague in a large western city. When my diagnosis of coronary thrombosis was mentioned, the colleague emphatically said that neither Dr. Herrick nor any one else was justified in making such a diagnosis except on the autopsy table. The attempt was ridiculous because it was impossible. The instructive and pathetic sequel to this is that, some ten or twelve years later, this same physician called me by telephone and in a feeble voice and in evident alarm told me he had just had an attack of coronary thrombosis, and what would I advise? He would send the electrocardiograms to me at once. Two or three years later a recurrent attack and a necropsy showed that his intra-vitam diagnosis had been correct.

In reaching conclusions regarding this subject I tried to be conservative. To this end the cases that weighed the heaviest were those with necropsy examination. A British writer (the reference has escaped me) some time after interest in coronary occlusion had begun to appear in England, wrote in a journal that the American physician had a great advantage over the British, as in the United States autopsies in public hospitals were far more readily obtained than in England. He did not realize that in the first two cases the post-mortem examinations had been made in the homes of well-to-do patients, and that the third was on a private patient in a hospital that was in no sense a public

institution. That autopsies on private patients are frequently secured if they are asked for is not as widely known as it should be. This statement applies to this country as well as to Great Britain.

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On March 28, 1918, a meeting of the Institute of Medicine of Chicago was held at the LaSalle Hotel, at which time the following program was presented:

SYMPOSIUM ON ANGINA PECTORIS

"Angina Pectoris; Personal Experiences of One of Our Members," by E. Fletcher Ingals; read by Ludvig Hektoen
"Pathology of Angina," by Edwin R. LeCount
"Coronary Thrombosis in Relation to Angina," by James B. Herrick
"Clifford Allbutt's Views in Regard to the Etiology of Angina," by Robert H. Babcock

The paper of Dr. Ingals was read by Dr. Hektoen because the author himself was too ill to be present. Dr. Ingals' discussion of angina was based on his experience with the condition in his practice. He described in detail the case of "Dr. X," who, as was generally known, was Dr. Ingals himself.

Dr. LeCount's paper was based on a careful study of "some sixty deaths from difficulties with the circulation of blood in the coronary arteries or with lesions generally regarded as caused by such difficulty. These are in two groups: thirty-four deaths from fibrous myocarditis with sclerosis of the coronary arteries, and twenty-six of more or less acute occlusion."

Dr. LeCount, as physician to the Coroner's office, had had an unusual experience with sudden and unexplained deaths, the "coroner's cases" that for medicolegal reasons require a postmortem examination. He had utilized the opportunity afforded him to make a scientific study of these cases, the results of which he embodied in this important contribution.

In my remarks I epitomized my views on the relation of coronary disease to angina, and discussed coronary occlusion and its clinical features. I repeated much of what had been stated in my 1912 paper, expressing views that, with minor differences, agreed with those of Dr. LeCount. Lantern slides were shown, illustrating the results of Dr. Smith's experimental work. The arguments I advanced and even the wording were much the same as those presented a few weeks later at Atlantic City.

Dr. Babcock spoke at length concerning Sir Clifford Allbutt's theory of angina pectoris, which he was strongly inclined to endorse.

On April 30, 1918, a little more than four weeks after his paper had been read, Dr. Ingals died. A little later, Dr. LeCount, in his report of the necropsy he had made on the body of Dr. Ingals, commented that he found nothing in this examination to support the position of Dr.

Ingals in his adherence to the aortic theory of angina pectoris that had been advanced by Sir Clifford Allbutt.

The papers on angina and coronary disease were published in the *Proceedings of the Institute of Medicine* **2**: 65, 1918. An abstract is also found in the *Journal of the American Medical Association* **70**: 974, 1918. Dr. LeCount's paper, "Angina Pectoris: Report of a Post-Mortem Examination," is in the same volume of the 1918 *Proceedings of the Institute of Medicine*, page 77.

These papers apparently attracted little attention. The explanation is probably that the subject was not at that time one in which the profession was particularly interested. Perhaps also the fact that the Institute of Medicine was young, and its *Proceedings* had a very limited circulation, may be a partial explanation.

It has been a matter of personal regret that I failed to insert in my paper on "Thrombosis of the Coronary Arteries"[7] that I read May 8, 1918, before the Association of Physicians, a reference to LeCount's work. My paper, however, was already in final typewritten form, already announced—and, as I recall, abstracted—on the program of the Association. The omission of reference to LeCount's work was unintentional; but I learned long afterwards that he felt that he had been undeservedly slighted.

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There is surely no need to continue this intimate recital of my personal relations to the subject of disease of the coronary artery. Soon after the second paper on "Thrombosis of the Coronary Arteries" had been read, American physicians at the bedside and in the laboratory took up the work, and there was a veritable flood of articles on this topic. I participated, chiefly on the clinical side, and contributed several papers, in addition to delivering many unrecorded talks before students and groups of practitioners.[9]

Of course, I am responsible for all statements of facts, and their interpretation, that are contained in this paper. The major responsibility, however, for deciding to write and publish now, must rest with my three friends who for so long urged me to put these facts on record.

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THE PRECORDIAL ELECTROCARDIOGRAM

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INTRODUCTION.—Considerable progress has been made in the standardization of precordial leads, but there is still a great diversity of opinion as to how many leads of this kind should be taken, as to what precordial points should be explored, and as to the proper location for the remote or reference electrode. The multiplicity of leads still in use and still being recommended is the source of much confusion and continues to retard progress in the setting up of adequate normal standards and satisfactory diagnostic criteria applicable to the interpretation of the precordial electrocardiogram. It is not, therefore, surprising that there has been a persistent demand that a single standard method for taking precordial leads be established. Unfortunately, it is not easy to meet this demand for there is no generally accepted method for determining which leads are likely to prove most and which least useful, and there are very great differences of opinion as to whether the decisions required should be made on empirical grounds alone, or, if not, as to what general principles should be taken into consideration.

It seems to us that it would be less difficult to solve this problem if there were a more widespread and clearer understanding of the nature of precordial leads, the relations between them and leads of other kinds, the considerations which led to their use, the advantages which have made them popular, and the purposes which they may be expected to serve. We propose, therefore, to discuss the precordial and other special leads which we have used with much satisfaction over a long period. We want to emphasize the principles upon which they are based and to call attention to the kind of information that may be obtained by their use in cases of bundle branch block, ventricular hypertrophy, and myocardial infarction. It is in these conditions particularly that the standard limb leads have been found inadequate.

It is true that much of our present knowledge of the human electrocardiogram has been gained by the correlation of electrocardiographic data and clinical or post-mortem observations. Nevertheless, electro-

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Much of the work upon which this article is based was done with the aid of a grant from the Horace H. Rackham School of Graduate Studies.

This material was presented by Frank N. Wilson at the fifty-third annual meeting of the Association of Life Insurance Medical Directors of America held Oct. 21 and 22, 1942, and has been published in the Transactions of that Association (Vol. xxix, pp. 154-251).

Received for publication Oct. 16, 1943.

cardiography can hardly be considered a purely empirical science. Its physical and physiological foundations rest upon a large body of critical experimentation dictated by well-constructed hypotheses. These foundations were laid, and the more fundamental principles upon which the interpretation of electrocardiographic records is based were established, before the string galvanometer was introduced into clinical medicine. The more important advances made since that time have come about in the same way as those which preceded them. Few major electrocardiographic problems have been solved by clinical observations alone. For this there are excellent reasons. Our basic knowledge of action currents was acquired by means of direct leads from the tissues under investigation. Unfortunately, it was not possible to study the action currents of the human heart by this method, and indirect leads were necessarily employed for this purpose. The standard limb leads now in universal use have become indispensable, and they are entirely adequate for most of the purposes which clinical electrocardiograms can be expected to serve. They are not, however, capable of furnishing detailed information of the sort obtained when the surface of the exposed heart is explored by means of direct leads. Experiments on animals in which such leads have been employed have consequently continued to play a very important role in the solution of our most difficult electrocardiographic problems. We have not, however, been able hitherto to use all the knowledge acquired in this way to the best possible advantage, because the difference in character between the limb leads used in man and the direct leads used in animal experiments has made it difficult to correlate our clinical and experimental observations. Precordial leads of the type now widely used are much more closely related to direct leads than to the standard limb leads. It is precisely for this reason that they are of such great value. They not only detect lesions which are beyond the range of the standard limb leads, but furnish data that can be directly compared with the data obtained by the use of epicardial leads in animals.

Unipolar Direct Leads.—For the study of cardiac action currents, all kinds of direct leads are not equally satisfactory. In their extensive and detailed study of the course of the excitatory process over the ventricular muscle, Lewis and Rothschild[1] found that it was difficult or impossible to interpret the records obtained when both electrodes were in contact with the ventricular surface. When leads of this kind were used, the cardiac impulse spreading through the ventricular wall from within outward often reached both electrodes at approximately the same time. The deflections recorded under these circumstances were of complicated and variable form and gave no reliable clue to the time of arrival of the impulse beneath either electrode. When, on the other hand, a small electrode in contact with the epicardium was paired with an electrode on the chest wall, the QRS complex almost invariably

displayed a large and very abrupt deflection which was easily recognized and was found to coincide with the activation of the muscle in contact with the exploring electrode. The name "intrinsic deflection" was therefore assigned to it. The other deflections of the QRS group, which were attributed to the excitation of muscle more distant from this electrode, were referred to as "extrinsic deflections," but their origin was not studied in detail.

Because of the character of the laws which govern the distribution of electric currents in three-dimensional conductors such as the body,[2] the magnitude of the potential variations produced by the heartbeat at any point outside the heart itself rapidly diminishes as the distance from the epicardial surface increases. In the course of a cardiac cycle, the variations in potential at a point on the ventricular surface are in the neighborhood of thirty times as large as those displayed by the arms and legs. The deflections of leads from the ventricular surface to some distant part of the body, such as those employed by Lewis and Rothschild, represent the potential variations of the electrode in contact with the heart; the potential variations of the distant electrode are negligible by comparison. It is convenient to use the term "unipolar" to designate leads of this kind in which one electrode is almost completely indifferent, and the term "bipolar" to designate leads like the standard limb leads in which the two electrodes are approximately equidistant from the heart and may, in general, be expected to undergo potential variations of about the same magnitude.

The electrocardiograms reproduced in Fig. 1 were obtained by means of unipolar direct leads from the exposed heart of a dog. Six points on the anterior surface of the ventricle, easy to identify later by their relations to the vessels or other surface markings, were selected, and, from these, control curves were taken with a small exploring electrode. Points *7*, *6*, and *8* were on the right ventricle; the first was on the thickest part of the wall near the atrioventricular groove, and the other two were in the central region close to the trabeculated area which overlies the attachment of the anterior papillary muscle. Points *3*, *1*, and *2* were on the left ventricle; the first was very close to the junction of the free wall and septum, the second near the left margin of the heart, and the third very near the apex. After the control records had been taken, temporary right bundle branch block was produced by pressing upon the right side of the septum above the anterior papillary muscle with the back of a small knife thrust through the wall of the conus arteriosus just below the pulmonary valve. A second set of curves was taken immediately after the knife was withdrawn, and a third set when the right bundle branch had recovered almost completely. Left branch block was then produced by making a cut on the septum just beneath the aortic valve, and a fourth set of records was made. Standard Lead I was taken simultaneously with each direct lead. The intrinsic deflection is easily identified in all of the curves except the first and third from

point *7;* it is the sudden downward movement which begins with the peak of R. The beginning of this deflection, and therefore the peak of R, marks the time of activation of the subepicardial muscle in contact with the exploring electrode. Whether the activation of this muscle and the beginning of the intrinsic deflection coincide exactly or only approximately need not concern us here. It will be noted that, in the leads from the right ventricle, the peak of R fell very late in the QRS interval when right branch block was present and at the very beginning of this interval when left branch block was present. In the leads from points *1* and *2* on the left ventricle these relations are reversed; the peak of R fell late in the QRS interval when left branch block was present and early when right branch block was present. No curve was obtained from point *3* while right branch block was present, for the form of the ventricular deflections of Lead I shows that, when the second tracing was taken from this point, the right bundle branch had already recovered its conductivity. In the lead from point *3* taken after left branch block was produced, the peak of R was not later than before. This point was very close to the septum, and, in our experience, the intrinsic deflection in leads from this region has seldom been much delayed either by left or by right branch block.

When the cardiac mechanism is normal, the intrinsic deflection is always earliest in leads from the trabeculated region, as in the present instance (point *8*). It is only a very little later in leads from the central region but considerably later in leads from points near the atrioventricular groove (point *7*) and from points on the conus arteriosus. The earliest intrinsic deflections found on the left ventricle usually occur in leads from the apex (point *2*), the latest, in leads from the lateral part of the free wall toward the base. This region was not studied in the experiment under consideration. The intrinsic deflection is normally considerably later over the surface of the left ventricle as a whole, than over the surface of the right. This difference is attributable to the greater thickness of the left ventricular wall, for in general the latest intrinsic deflections are found where the muscle is thickest.

Origin of the QRS Deflections.—The origin of the more conspicuous and more constant components of the various kinds of ventricular complexes seen in unipolar direct leads is clearly understood. It must be emphasized that, although the excitation of the muscle in contact with the exploring electrode produces a much larger and much more sudden fluctuation in the potential of this electrode than the excitation of any equal mass of muscle at a greater distance from it, every unit of ventricular muscle, without exception, produces action currents which contribute to the form of these complexes. It is obvious that those components of the QRS complex which precede the intrinsic deflection must be attributed to the excitation of muscle which passed into the active state ahead of the subepicardial muscle beneath the exploring electrode,

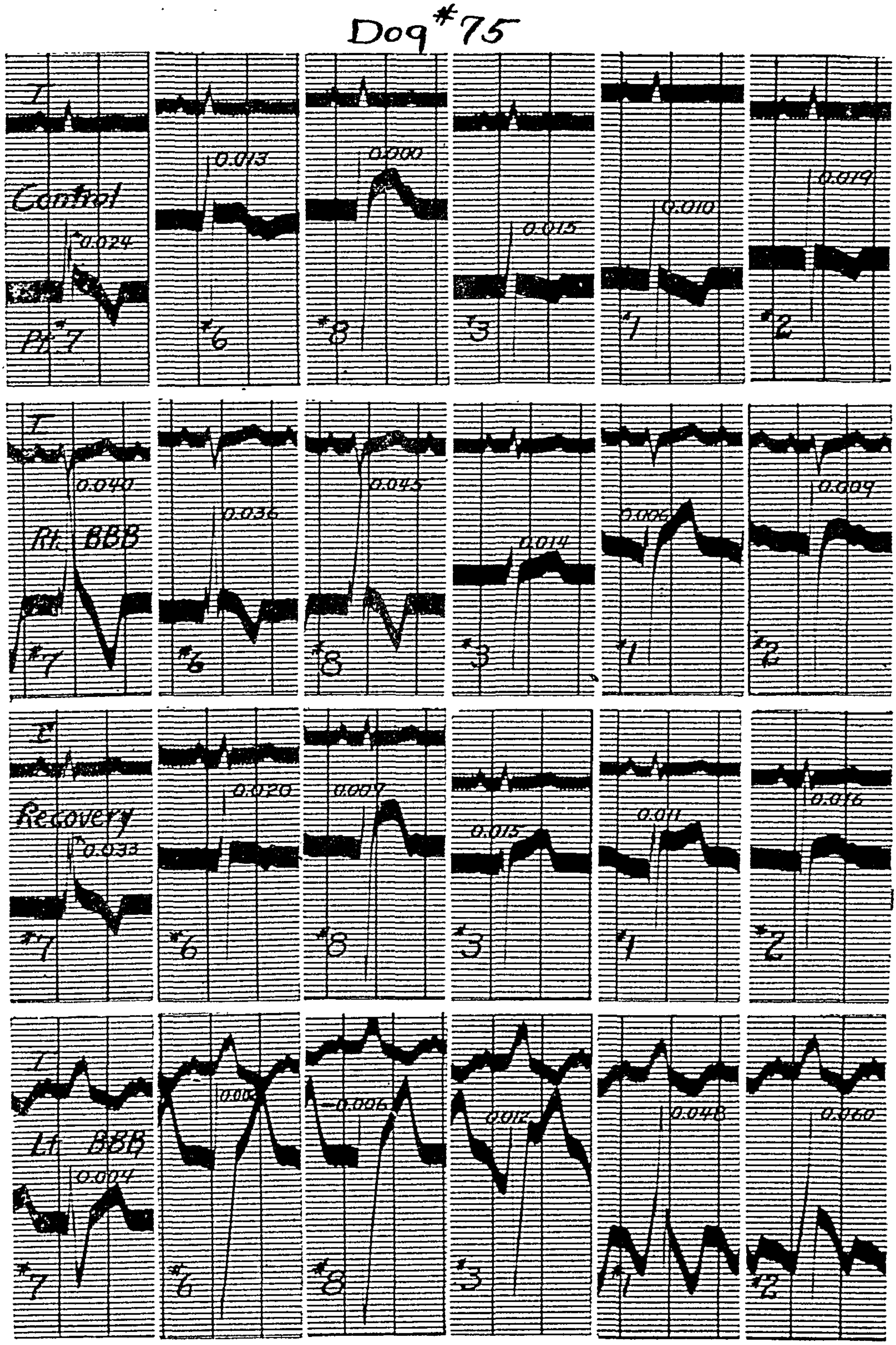


Fig. 1.—Unipolar direct leads from six points on the exposed ventricular surface of a dog's heart.

and that those components which follow the intrinsic deflection must be ascribed to the excitation of muscle that was still in the resting state when the muscle under the contact became active. The peak of R, therefore, separates the QRS components attributable to muscle activated before, from the QRS components attributable to muscle activated after, the cardiac impulse reached the muscle in contact with the exploring electrode.

The resting cardiac muscle fiber is surrounded by a "membrane" which has a very low electrical conductivity. Across this membrane there is an electromotive force which makes its inner surface strongly negative in comparison with its outer surface. The passage of the excitatory process along the fiber is associated with a sudden and very great increase in the conductivity of the resting membrane and a sudden decrease in the electromotive force (Cole and Curtis[3]); in other words, with the sudden development of a short circuit between the inside and the outside of the fiber. Current flows out of the resting part of the fiber adjacent to the short circuit and re-enters the fiber through the short-circuited region. The effect in the medium outside the fiber is the same as if the cardiac impulse were immediately preceded by the positive pole, and accompanied by the negative pole, of a battery. In other words, we may say that, across the boundary between active and resting muscle, there is an electromotive force which makes the potential of points toward which the excitation wave is advancing positive, and the potential of points which lie behind it negative.

The cardiac impulse spreads through the free walls of the ventricles from within outwards and normally enters the septum from both sides simultaneously. Throughout its course it is traveling away from the ventricular cavities, and these are continuously on the negative side of all the boundaries between active and resting muscle. Consequently, the potential of both cavities is negative throughout the QRS interval[4] except in those instances in which one side of the septum becomes active before the other, in which case the ventricular cavity on the side activated last almost always displays initial positivity.

Electromotive forces distant from two neighboring points have approximately the same effect upon the potential of both. It is clear, then, that no cardiac electromotive force except that generated by the muscle between them is capable of producing a large difference of potential between two points which are separated solely by the thickness of the ventricular wall. If the potential of the adjacent part of the ventricular cavity is negative, the potential of an epicardial electrode can be positive only while the excitation wave is passing through the part of the ventricular wall upon which it rests. In taking unipolar leads the galvanometer connections are so made that positivity of the exploring electrode produces an upward deflection in the completed record. The R deflection in unipolar leads from the ventricular epicardium of the

normal heart must, therefore, represent the electrical forces produced by excitation of the muscle between the exploring electrode and the ventricular cavity. The total voltage of these forces is, of course, not measured by the height of the R deflection, but by the difference in potential between the endocardial and the epicardial surfaces of that part of the ventricular wall in contact with the exploring electrode. In bundle branch block most, if not all, of the septal muscle is activated from the contralateral side, and the potential of the homolateral cavity is positive until the cardiac impulse has passed through the septum. Under these circumstances, the R deflection in leads from the outer surface of the delayed ventricle ordinarily displays two peaks. The part of this deflection which precedes the division is due to activation of the septum and represents positivity of the ventricular cavity which is transmitted through the inactive ventricular wall; the part which follows the division is due to activation of the ventricular wall adjacent to the electrode. When this second peak of R is written, the ventricular cavity is negative.

When the excitatory process reaches the muscle in contact with an epicardial electrode, the boundary between resting and active muscle disappears from that part of the ventricular wall upon which the electrode rests. The potential of the electrode then becomes the potential of the adjacent part of the ventricular cavity. The sudden drop in the potential of the electrode when the electromotive force across the wall beneath it disappears is responsible for the intrinsic deflection. The total length of this deflection is an approximate measure of the voltage across the ventricular wall when the cardiac impulse arrived at the epicardial surface.

If the excitatory process is still spreading through some part of the ventricular wall when the intrinsic deflection occurs, the negativity of the ventricular cavity outlasts this deflection and an S wave is inscribed. If, on the other hand, the muscle in contact with the exploring electrode is the last ventricular muscle to pass into the active state, the ventricular cavity is at zero potential when the intrinsic deflection is complete and there can be no S deflection.

If the subendocardial muscle of some part of the ventricular wall passes into the active state earlier than the subendocardial muscle which lies between the exploring electrode and the ventricular cavity, the initial negativity of the cavity is transmitted to this electrode and a Q deflection occurs. If the cavity is initially positive because of circumstances that we have already mentioned, there can be no Q. Since late activation of the subendocardial muscle is likely to be associated with late activation of the subepicardial muscle of the same region, Q deflections are most common in those leads in which the intrinsic deflection occurs late in the QRS interval, and in which, therefore, R is tall and S is small or absent.

In summarizing our remarks on the interpretation of the QRS deflections of unipolar direct leads from the ventricular surface, we may point out that the character of these deflections depends mainly upon the time at which the muscle in contact with the exploring electrode becomes active in relation to the beginning and to the end of the QRS interval. If this muscle becomes active very early in this interval, the R deflection is narrow and usually small and the S wave broad and usually deep. If it is activated very late in this interval, R is tall and broad, S small and narrow, and a Q wave is often present. If it is activated at the very end of the QRS interval, S is absent but there may be a conspicuous Q. As the time of activation of the muscle beneath the exploring electrode approaches the beginning of the QRS interval, R becomes smaller, S larger, and Q less frequent. As it approaches the *end of the QRS interval, R becomes larger, S smaller, and Q more frequent.* In this discussion we have, of course, not considered many of the perplexing details of the QRS complex which may be encountered in unipolar direct leads as well as in leads of other kinds. Some of these cannot be interpreted satisfactorily until more data are available than at present.

Unipolar Precordial Leads.—The potential of every extracardiac point inside the body is determined by the potential over the heart's outer surface. The potential variations of every element of the epicardial surface contribute in some measure to the potential variations of an electrode placed upon the precordium. But the magnitude of the contribution made by the potential variations of any given surface element is large if its distance from the electrode is small, and vice versa; in fact, it varies roughly as the inverse cube of this distance. For this *reason, the potential variations of a precordial electrode are determined* to a very large extent by the potential variations of the elements of ventricular surface nearest it. If all or the great majority of these elements simultaneously display potential variations of the same sort, the potential variations of the electrode are of the same character though very much smaller. If, on the other hand, the various elements that are more or less equidistant from the electrode display potential variations of many different kinds, the potential variations of the electrode represent a mixture which may not resemble any of its components very closely.

Since the conditions last mentioned rarely exist, it is almost always possible, by moving an electrode step by step across the precordium, to determine the nature of the potential variations of the various parts of the anterior ventricular surface, provided that the potential variations of the exploring electrode are accurately recorded. In 1929 we began to use multiple precordial leads of this kind to ascertain which of the two ventricles first became active in the classical varieties of bundle branch block. In our first experiments the precordial electrode was paired with an electrode on the left leg. The data obtained in this

way were not entirely conclusive because the components of the QRS complex due to potential variations of the precordial electrode could not be distinguished with certainty from those due to potential variations of the leg electrode.

In man, the potential variations of the precordium are ordinarily three to five times as large as those of the extremities or of the back. When a precordial electrode is paired with an extremity or dorsal electrode, the general outline of the ventricular complex is determined, therefore, to a very large extent by the potential variations of the former and is much the same regardless of whether the latter is placed upon the right arm, the left arm, the left leg, or the left infrascapular region. But in leads of this kind the potential variations of the reference electrode do exert a very considerable influence upon the details of the form of the ventricular complex and make it impossible to utilize the simple principles applicable to the interpretation of the deflections of *unipolar direct leads* in the analysis of the records obtained.

Many seem to believe that precordial leads are merely additional leads comparable in all respects to the standard limb leads. The practice of taking a single precordial lead and calling it Lead IV, a practice which we have never followed, is no doubt partly responsible for this entirely unjustifiable attitude. There is no limit to the number of pairs of points on the trunk which might have served as locations for the electrodes if the "cut and try" method had been used to find the additional leads most likely to prove helpful in those situations in which limb leads had been found inadequate. Precordial leads of the kind under consideration were selected for this purpose because observations dictated by theoretical considerations showed that they are in reality semidirect leads from the anterior ventricular surface, capable within certain limits of serving the same purposes as direct leads from the ventral wall of the exposed heart. They cannot serve these purposes, however, unless the potential variations of the reference electrode are made negligibly small in comparison with those of the exploring electrode. The extent to which the character of the potential variations of the precordial electrode is obscured by the potential variations of the remote electrode determines the degree to which the advantages gained by placing one electrode upon the precordium have been surrendered.

Considerations of this kind led us to devise an artificial ground which reduces the potential variations of the remote electrode to a minimum and makes it possible to obtain essentially unipolar leads from the precordium, from the esophagus, from the extremities, and from other parts of the body. This artificial ground consists of a central terminal which is connected through three equal resistances of 5,000 ohms each to electrodes on the right arm, left arm, and left leg.[5] The effect of this device is to balance out those electric forces responsible for differences in potential between these extremities and consequently for the deflec-

tions of the standard limb leads. It is easily demonstrated that at every instant the potential of the central terminal must be equal to the algebraic mean of the potentials of the three extremity electrodes. On the basis of the assumptions upon which Einthoven's equilateral triangle is founded it has been shown that those components of the heart's resultant electromotive force which are parallel to the plane defined by this triangle have no effect whatever upon the potential of the central terminal. The effects of those components which are perpendicular to this plane cannot be accurately predicted on theoretical grounds. The experiments of Eckey and Fröhlich,[6] Burger,[7] Burger and Wuhrmann,[8] and of others[9] have, however, demonstrated that the largest potential variations of the central terminal do not ordinarily exceed 0.3 millivolt. The potential of this terminal is, therefore, so nearly constant that for practical purposes we may consider it zero throughout the cardiac cycle. We shall then consider all leads unipolar in which an exploring electrode is paired with an artificial ground of this type.

When we began to use precordial leads in our studies of human and experimental bundle branch block, it soon became evident that the most satisfactory way to obtain semidirect leads from both ventricles was to move the exploring electrode across the precordium, along a line roughly perpendicular to the anterior interventricular sulcus and extending from a point at least as far to the right as the right margin of the sternum to a point well beyond the left border of the heart. We have changed our original method of taking precordial leads only as regards the number and the locations of the points explored, which have undergone minor modifications from time to time. We now take unipolar leads from each of the six points specified by the Committee of the American Heart Association for the Standardization of Precordial Leads.[10] In accordance with the recommendations of this committee, these leads are designated V_1, V_2, V_3, V_4, V_5, and V_6. The first of these six points is at the right margin of the sternum in the fourth intercostal space and the second on the left sternal margin at the same level. The remaining points lie on a broken line extending from the second point to the apex beat and thence around the left side of the chest at the apical level. When the apex beat cannot be located, this line is drawn from the second point to the intersection of the left midclavicular line and the fifth intercostal space and is continued around the chest at the level of this intersection. The third point is midway between the second and the left midclavicular line, the fourth in the midclavicular line, the fifth in the anterior axillary line, and the sixth in the midaxillary line. In addition to these six standard leads, we usually take a unipolar lead from the tip of the ensiform cartilage (Lead V_E) and often take unipolar leads from the posterior axillary line (Lead V_7), from the left infrascapular region (V_B), and from other points.

In the precordial electrocardiograms of normal subjects the ventricular complexes of the leads from the right side of the precordium are

strikingly similar to those obtained by placing the exploring electrode directly upon the thinner parts of the anterior wall of the dog's right ventricle (Fig. 2). In these complexes the R deflection is small and narrow and S is deep and relatively broad. The peak of R occurs early in the QRS interval and is followed by a large, abrupt downward movement which obviously corresponds to the intrinsic deflection of direct leads. The ventricular complexes of the leads from the left side of the precordium are similar to those seen in direct leads from the thicker parts of the anterior and left lateral walls of the dog's left ventricle.

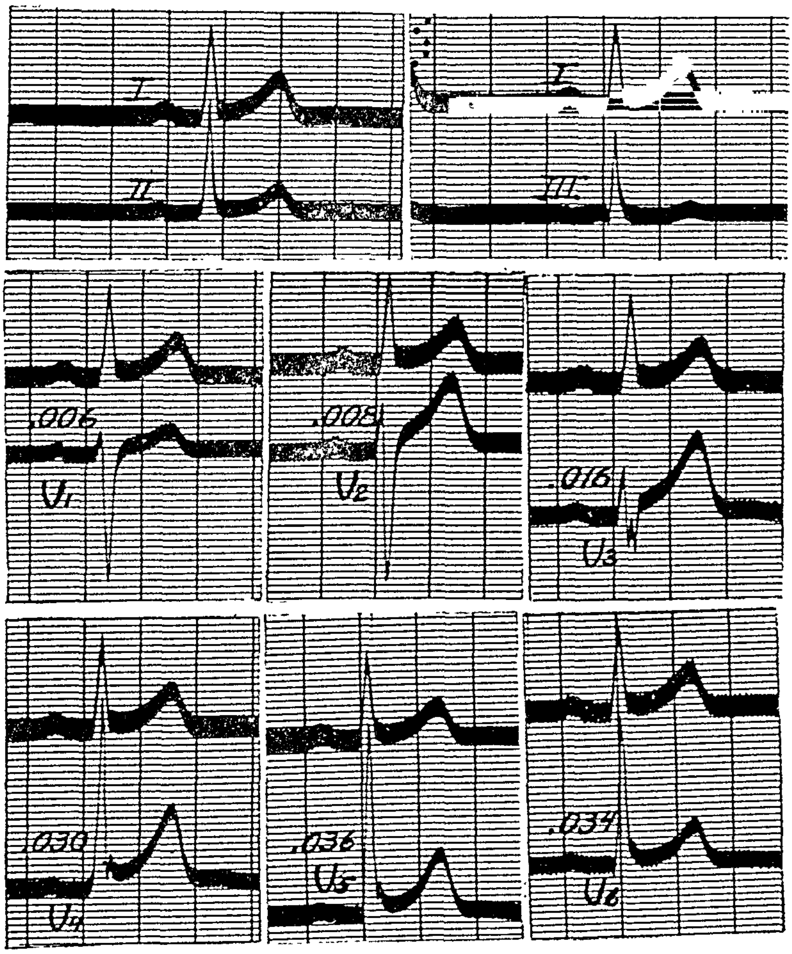


Fig. 2.—The precordial electrocardiogram of a normal subject. The decimals marked on each record give the time of the intrinsic deflection with reference to the beginning of the QRS interval in Lead I, which was taken simultaneously with each precordial lead. (Reproduced from an article by Wilson in Stroud's *Diagnosis and Treatment of Cardiovascular Disease,* by permission of the F. H. Davis Company, Philadelphia.)

The R component of these complexes is tall and relatively wide and it is often preceded by a Q and followed by an S deflection. The peak of R which marks the onset of the intrinsic downstroke is, on the average, about 0.02 second later in leads from the left side of the precordium than in leads from the right side.[11] In precordial leads this downstroke is not nearly so sudden as in direct leads and, therefore, is somewhat more difficult to identify with certainty when the contour of the ventricular complex is complicated or unfamiliar.

TABLE I

THE SIZE OF THE VENTRICULAR DEFLECTIONS IN THE STANDARD AND SPECIAL LEADS (MEASUREMENTS GIVEN IN TENTHS OF A MILLIVOLT)

LEAD	Q				R				S				T				RS			
	MINIMUM	MAXIMUM	MEAN	STANDARD DEVIATION	MINIMUM	MAXIMUM	MEAN	STANDARD DEVIATION	MINIMUM	MAXIMUM	MEAN	STANDARD DEVIATION	MINIMUM	MAXIMUM	MEAN	STANDARD DEVIATION	MINIMUM	MAXIMUM	MEAN	STANDARD DEVIATION
I	0	1.5	0.33	0.45	1.5	19.4	6.81	3.27	0	5.0	1.67	1.35	1.0	5.5	2.21	1.05	3.0	20.6	8.63	3.20
II	0	2.0	0.43	0.61	4.0	22.0	11.99	4.39	0	8.0	1.53	1.92	1.0	6.0	2.97	1.10	8.0	23.0	13.76	3.72
III	0	2.0	0.54	0.60	1.2	18.0	8.50	4.33	0	13.0	1.27	2.40	0	3.0	1.49	0.75	3.2	18.0	10.12	4.10
V_R	0	7.6	2.81	2.68	0	3.0	0.76	0.65	0	10.5	2.56	3.41	-3.3	-0.8	-1.66	0.61	3.5	11.7	6.30	1.82
V_L	0	1.5	0.21	0.42	0	7.0	1.13	1.34	0	7.0	2.00	1.60	-1.0	1.0	0.05	0.41	0.5	8.5	3.27	1.85
V_F	0	1.2	0.29	0.37	0	13.0	6.68	2.81	0	6.5	0.80	1.28	0.2	2.8	1.46	0.62	4.0	13.0	7.66	2.54
V_1	0	0	0	0	1.0	9.6	4.16	2.33	3.4	24.0	11.05	5.03	-4.0	5.6	1.23	1.88	6.6	26.8	15.21	5.98
V_2	0	0	0	0	4.0	20.8	9.05	3.68	3.0	38.8	16.23	7.30	2.4	11.0	6.22	1.90	15.0	46.0	25.27	7.47
V_3	0	0.4	0.013	0.072	6.0	54.6	16.70	9.78	0	22.0	9.05	5.62	3.6	12.0	6.26	1.89	12.6	54.6	25.75	8.37
V_4	0	3.0	0.37	0.68	12.2	46.0	22.31	7.10	0	16.0	5.32	4.13	2.4	11.0	5.66	1.84	18.0	51.6	27.63	6.71
V_5	0	3.4	0.57	0.91	8.8	33.0	18.78	6.91	0	9.6	1.93	2.22	2.0	9.6	4.59	1.82	11.2	33.2	20.70	6.50
V_E	0	0	0	0	2.0	12.8	5.81	2.49	0	16.2	6.09	4.78	0.2	5.2	2.55	1.11	5.6	24.2	11.91	4.33

Between those parts of the precordium which yield small R and deep S waves and those which yield QRS complexes of the opposite kind, there is a zone which yields complexes that are intermediate in form or represent a combination of the deflections obtained at points farther to the right and those obtained at points farther to the left. This zone varies from subject to subject, both in location and in width, and is probably not absolutely constant in either particular in one and the same subject. The ventricular complexes of leads from this transitional zone may display notching and other peculiarities of form. They represent a mixture to which the potential variations of those parts of the right ventricle and the potential variations of those parts of the left ventricle which are least distant from the exploring electrode contribute in approximately equal measure.

The minimal, maximal, and mean voltages of Q, R, S, and T in precordial Leads V_1, V_2, V_3, V_4, V_5, and V_E, and in unipolar extremity Leads V_R, V_L, and V_F, found by Kossmann and Johnston[11] in their study of thirty normal subjects, are given in Table I, which is reproduced in modified form from their paper.

Unipolar Limb Leads.—Unipolar leads from the right arm (V_R), left arm (V_L), and left leg (V_F) furnish a valuable means of comparing the potential variations of these extremities with those of the right and left sides of the precordium and, consequently, of establishing relations between the complexes of the standard limb leads and those of the precordial leads. Unipolar limb leads may be taken by placing the exploring electrode used in taking the precordial leads on each of the extremities in turn or by transferring the wire connected to this electrode to each of the extremity electrodes. When this is done, the deflections obtained are often inconveniently small unless the sensitivity of the electrocardiograph is increased to one and a half or two times its normal value. Goldberger[12] has introduced a procedure which avoids this difficulty. By breaking the connection between the central terminal and the extremity upon which the exploring electrode has been placed, he increases the size of the deflections obtained by fifty per cent without changing the sensitivity of his apparatus. The standard limb leads and the unipolar limb leads are, of course, directly and simply related. The deflections of any two leads of either set furnish all the data needed to compute the deflections of the other four. The equations which express these relations have been published elsewhere[5] and need not be repeated here. It may be pointed out here, however, that when the ventricular complexes of Leads I and II are similar in form, the complexes of Lead V_R resemble the complexes of these leads turned upside down; that when the complexes of Lead III are the inverse of those of Lead I, the complexes of Lead V_L are like those of Lead I; and that when the complexes of Leads II and III are alike, those of Lead V_F have the same form. It should also be remembered that at any instant

the algebraic sum of the potentials of the three extremities is equal to zero.

The Position of the Heart From the Electrocardiographic Standpoint. —The standard and unipolar electrocardiograms of six subjects are reproduced in Fig. 3. Not all of these tracings are normal, but, so far

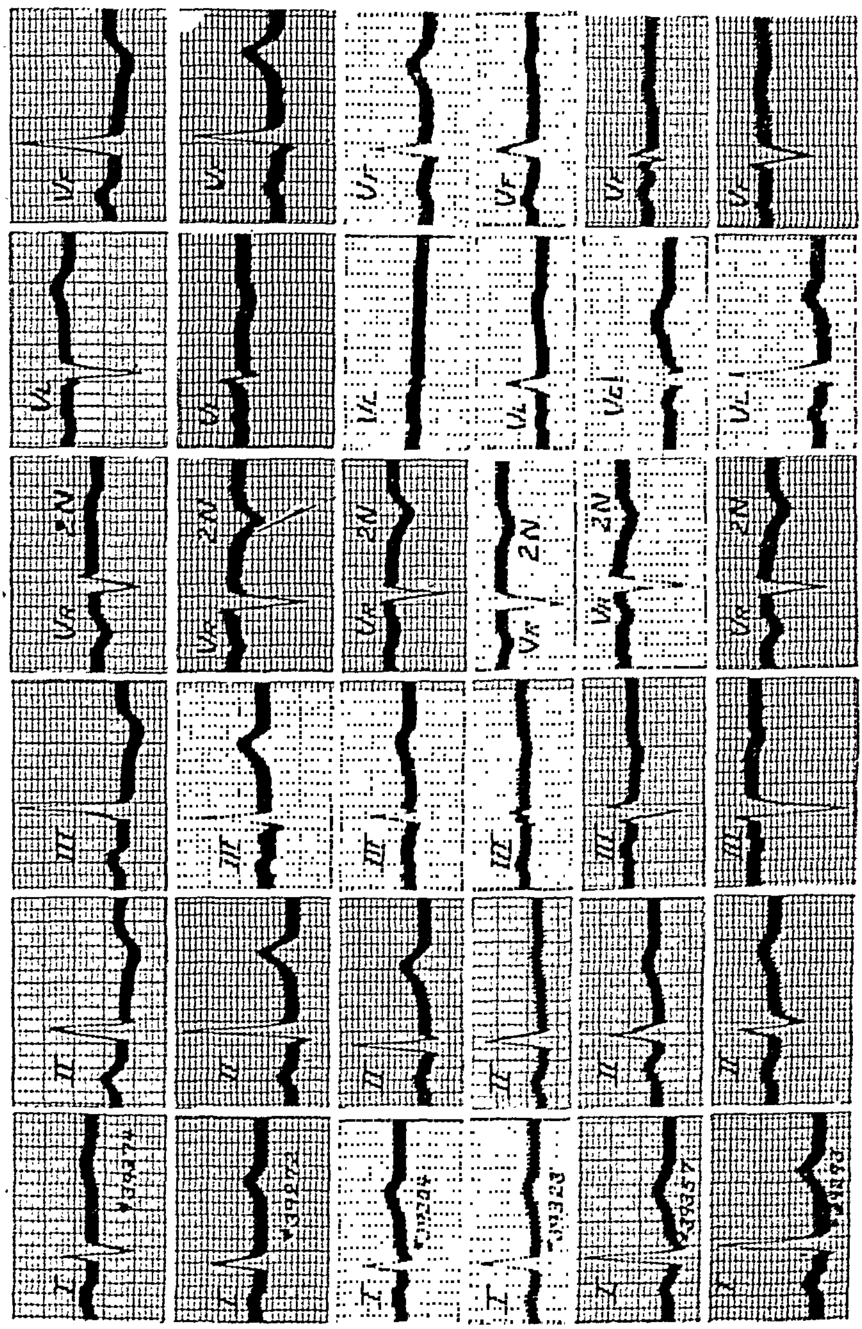


Fig. 3.—The bipolar (Leads I, II, and III) and unipolar (Leads V_R, V_L and V_F) electrocardiograms of six subjects arranged according to the position of the mean electrical axis of QRS. The unipolar limb leads were taken with the galvanometer at twice the normal sensitivity (2N). Assuming that the QRS deflections of the precordial leads, had they been taken, would have been of the normal type, the heart was in the vertical position in the first, in the semivertical position in the second and third, in the intermediate position in the fourth, in the semihorizontal position in the fifth, and in the horizontal position in the sixth case. This figure appeared in an article by Wilson, Johnston, Cotrim, and Rosenbaum.[13]

as the QRS complexes are concerned, similar curves could be selected from any collection of normal records. They are arranged in accordance with the position of the mean electrical axis of QRS; the one which displays the greatest degree of right axis deviation is at the top and the one which displays the greatest degree of left axis deviation is

at the bottom. It will be noted that the potential variations of the right arm (V_R) were always of the same general kind. In some cases, this extremity was slightly positive at the beginning, at the end, or both at the beginning and at the end of the QRS interval, but throughout by far the greater part of this interval it was conspicuously negative in all. The potential variations of the other two extremities varied greatly with the position of the electrical axis. When this axis was shifted to the right, as in the first electrocardiogram, the potential variations of the left arm (V_L) were like those which occur over the anterior surface of the dog's right ventricle and over the right side of the precordium in normal subjects. The potential variations of the left leg (V_F), on the other hand, resembled those which occur over the anterolateral surface of the dog's left ventricle and over the left side of the precordium in normal subjects. When the electrical axis was shifted to the left, as in the last electrocardiogram, just the reverse was the case; the potential variations of the left arm resembled those normally found on the left side of the precordium, and the potential variations of the left leg, those normally found on the right side.[13]

When the heart is normal, the precordial electrocardiogram has essentially the same form regardless of whether the limb leads display right axis deviation, no axis deviation, or left axis deviation. It is evident, therefore, that, in normal subjects with right axis deviation, the potential variations of the right ventricular surface are transmitted to the left arm and the potential variations of the left ventricular surface to the left leg, whereas, in normal subjects with left axis deviation, the potential variations of the right ventricular surface are transmitted to the left leg and the potential variations of the left ventricular surface to the left arm. These differences in the magnitudes of the contributions made by the right and left ventricular surfaces to the potential variations of arm and leg can hardly depend upon factors lying within the heart itself; they must be due to variations in the spatial relations between the surfaces of the two ventricles and the attachments of the extremities to the trunk. When the electrocardiogram is normal, there is an obvious correlation between the inclination of the mean electrical axis of QRS and the position of the heart. When the long axis of the heart is nearly vertical, right axis deviation is usually present, and when the long axis of the heart is nearly horizontal, left axis deviation is usually present. We are justified, therefore, in using the terms "vertical" and "horizontal" in defining the position of the heart from the purely electrocardiographic standpoint. So far as the normal heart is concerned, the first five of the six cardiac positions described below could be defined equally well in terms of the position of the electrical axis, but, if that were done, the definitions could not be applied when the heart was abnormal.

From the purely electrocardiographic standpoint, we may then define the following six positions of the heart (Fig. 3).

Vertical Position.—

a. The ventricular complexes of Lead V_L resemble those of Leads V_1 and V_2.

b. The ventricular complexes of Lead V_F resemble those of Leads V_5 and V_6.

Semivertical Positions.—

a. The ventricular complexes of Lead V_F resemble the ventricular complexes of Leads V_5 and V_6.

b. The QRS deflections of Lead V_L are small.

Intermediate Position.—

a. The ventricular complexes of Leads V_L and V_F are similar in form and size and like those of Leads V_5 and V_6.

Semihorizontal Position.—

a. The ventricular complexes of Lead V_L resemble those of Leads V_5 and V_6.

b. The QRS deflections of Lead V_F are small.

Horizontal Position.—

a. The ventricular complexes of Lead V_L resemble those of Leads V_5 and V_6.

b. The ventricular complexes of Lead V_F resemble those of Leads V_1 and V_2.

Indeterminate Position.—There is no obvious relationship between the ventricular complexes of the limb leads and those of the precordial leads.

As long ago as 1910, Kraus and Nicolai[14] asserted that the deflections obtained by leading from the surface of the body are very similar to those that would be obtained by leading from those parts of the heart's surface beneath and nearest the electrodes. They based this opinion upon the principles that govern the distribution of electric currents in volume conductors. As regards precordial leads, we reached a similar conclusion long before we knew that others had held this view, and we have demonstrated that there is a very close relation between the potential variations of a precordial electrode and the potential variations of the underlying ventricular surface. There is considerable evidence of a less direct kind that the potential variations of the right arm are similar to the potential variations of those parts of the heart's surface that are nearest the right shoulder; that the potential variations of the left arm resemble the potential variations of those parts of the heart's surface that are nearest the left shoulder; and that the potential variations of the left leg are like the potential variations of the heart's diaphragmatic surface.

We have already mentioned that the potential of the right arm is ordinarily negative throughout the greater part of the QRS interval. The reason lies in the relation of the right shoulder to the great valvular

orifices at the base of the heart. The negativity of the ventricular cavities is transmitted through these orifices to the adjacent parts of the body, including the right shoulder and the right arm. The potential variations of this extremity do not represent the potential variations of the ventricular cavities in pure form, of course, but mixed with the potential variations of other regions and particularly with those of the surface of the right ventricle. Over the thinner parts of the free wall of this chamber, the potential is normally weakly positive at the very beginning of the QRS interval, but during the rest of this interval it does not differ from that of the ventricular cavity. It is frequently impossible, therefore, to say whether the base of the heart or the right ventricular surface contributed most to the potential variations of the right arm. The same is sometimes true with reference to the potential variations of the left arm. It is well known that when the heart assumes a more vertical position or turns about its long axis in the direction required to bring the left ventricle below the right, the potential variations of the left leg become more like those of the left ventricular surface and less like those of the right ventricular surface, while the potential variations of the left arm change in the opposite way. When the heart assumes a more horizontal position or twists about its long axis in the direction required to bring the right ventricle below the left, the effects upon the potential variations of the left arm and left leg are the reverse of those described.

It is also true that, in myocardial infarction, the potential variations that occur at the epicardial surface of the infarct are transmitted to the left arm when the anterolateral wall of the left ventricle is involved and to the left leg when the diaphragmatic wall is involved.

But although the anatomical position of the heart and its electrocardiographic position are very closely related, there are reasons for believing that the correlation between the two cannot be perfect. It is evident that those parts of the right ventricular surface which play the most important role in determining the potential variations of the right side of the precordium are not identical with those parts of this surface which play the most important role in determining the potential variations of the left arm or left leg, as the case may be. A similar statement may be made with reference to those parts of the left ventricular surface which contribute most to the potential variations of the left side of the precordium. Significant relations between the ventricular complexes of the precordial leads, and the ventricular complexes of the unipolar limb leads of the kind upon which the determination of the electrocardiographic position of the heart is based, can be expected to occur, therefore, only when potential variations of one kind take place simultaneously over a large part of the right ventricular surface and potential variations of another kind take place simultaneously over a large part of the left ventricular surface. This is likely to happen

when the heart is normal, in right and in left bundle branch block, and in preponderant hypertrophy of the right or left ventricle. It is much less likely to happen when there are lesions which give rise to local modifications of the potential variations at the surface of the heart or

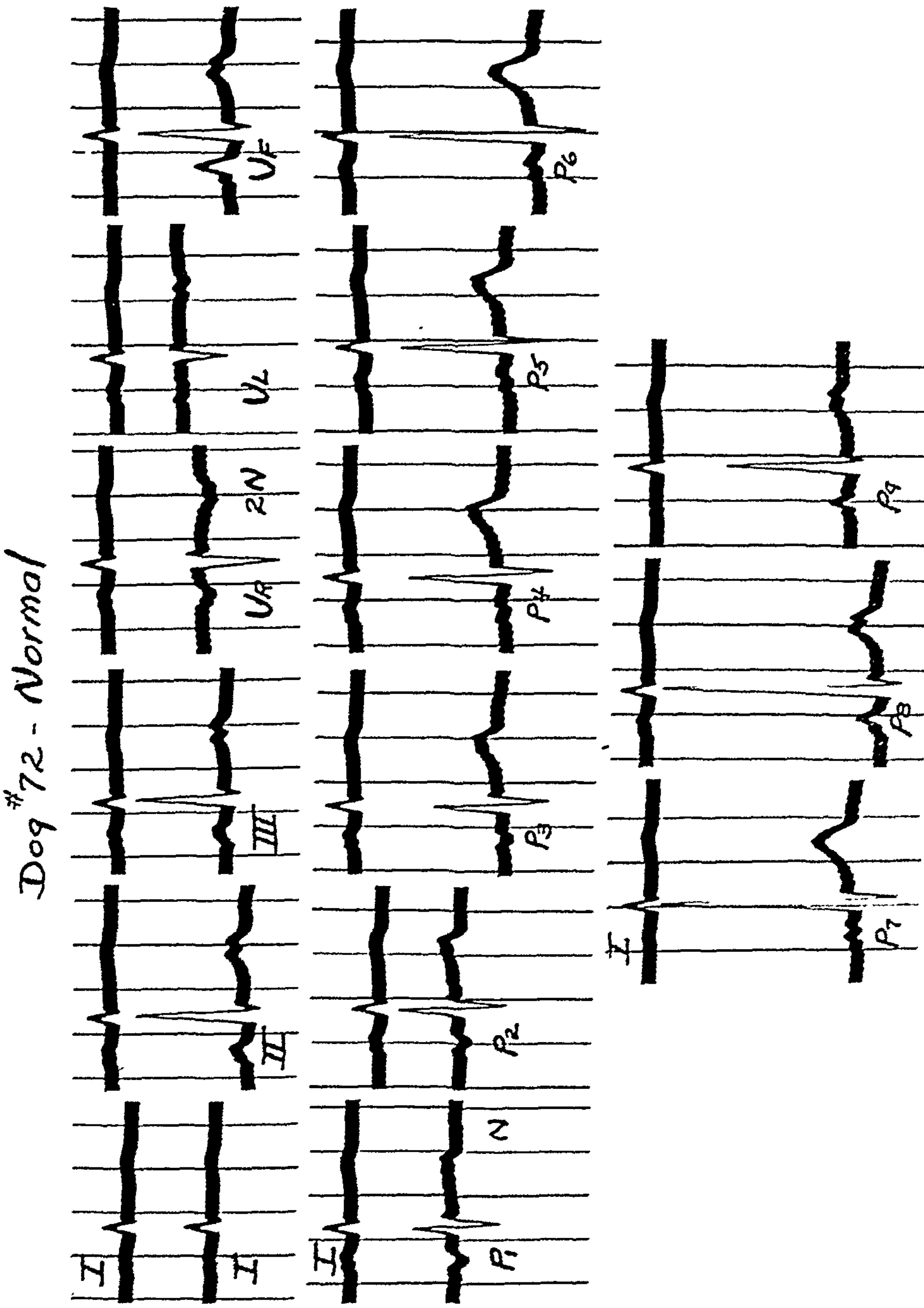


Fig. 4.—The standard electrocardiograms, unipolar electrocardiograms, and precordial electrocardiograms of a normal dog. The potential variations of the left hind leg (V_F) were similar to those of the left side of the precordium (P_7, P_8, and P_9).

which have opposite effects upon the potential variations of different parts of the surface of the same ventricle. For this reason and because the potential variations of the extremities often represent complicated mixtures, it is often impossible in cases of myocardial disease to establish any relation between the potential variations of the precordium and the potential variations of the extremities.

It should be noted that the electrocardiographic position of the heart may change even though the anatomical position remains the same. This is true because the former is determined not only by the orientation of the surfaces of the two ventricles, but also by the distribution of potential variations of various kinds on each of them. In bundle branch block, for example, the regions in which the same kind of potential variations occur at the same time are not exactly the same in extent and configuration as when the heart is normal. Consequently, the onset of bundle branch block may, although it usually does not, alter the position of the heart from the electrocardiographic standpoint.

The Precordial Electrocardiograms of Dog and Man.—The electrocardiograms reproduced in Fig. 4 represent observations made in the course of an experiment upon a normal dog. Standard limb leads, unipolar limb leads, and nine unipolar precordial leads were taken. The first precordial lead was from a point 4 cm., and the second from a point 2 cm., to the right of the midline; the other precordial leads were taken by moving the exploring electrode across the precordium in a base-apex direction and were from points 2 cm. apart. The precordial curves closely resemble the normal human curves obtained by the same method. The potential variations of the two forelegs were similar; both extremities were negative throughout the greater part of the QRS interval (Leads V_R and V_L). The ventricular complexes of Lead V_F are like those obtained from the left side of the precordium (Leads P_5, P_6, P_7, P_8, and P_9) and the deflections of Lead V_L are smaller than those of the other unipolar limb leads. The heart, then, was in the semivertical position.

The electrocardiograms shown in Fig. 5 are reproduced to demonstrate that there are no essential differences between the precordial electrocardiograms obtained in canine bundle branch block and those obtained in human bundle branch block. The curves of the first set represent left branch block in man; those of the second set left branch block in the dog. In both cases the ventricular complexes of the leads from the right side of the precordium display small R and broad S deflections, indicating that the excitatory process arrived at the surface of the right ventricle very early in the QRS interval. The ventricular complexes of the leads from the left side of the precordium, on the other hand, are dominated by broad notched R waves of the kind seen in direct leads from the anterolateral wall of the left ventricle after section of the left branch of the His bundle. The curves of the third set represent human right branch block, and those of the fourth set, canine right branch block. Here the complexes of the leads from the right side of the precordium display a small initial R and a tall final R deflection and are similar to those obtained by leading directly from the surface of the right ventricle after the right branch of the His bundle has been cut. The ventricular complexes of the leads from the left side of the

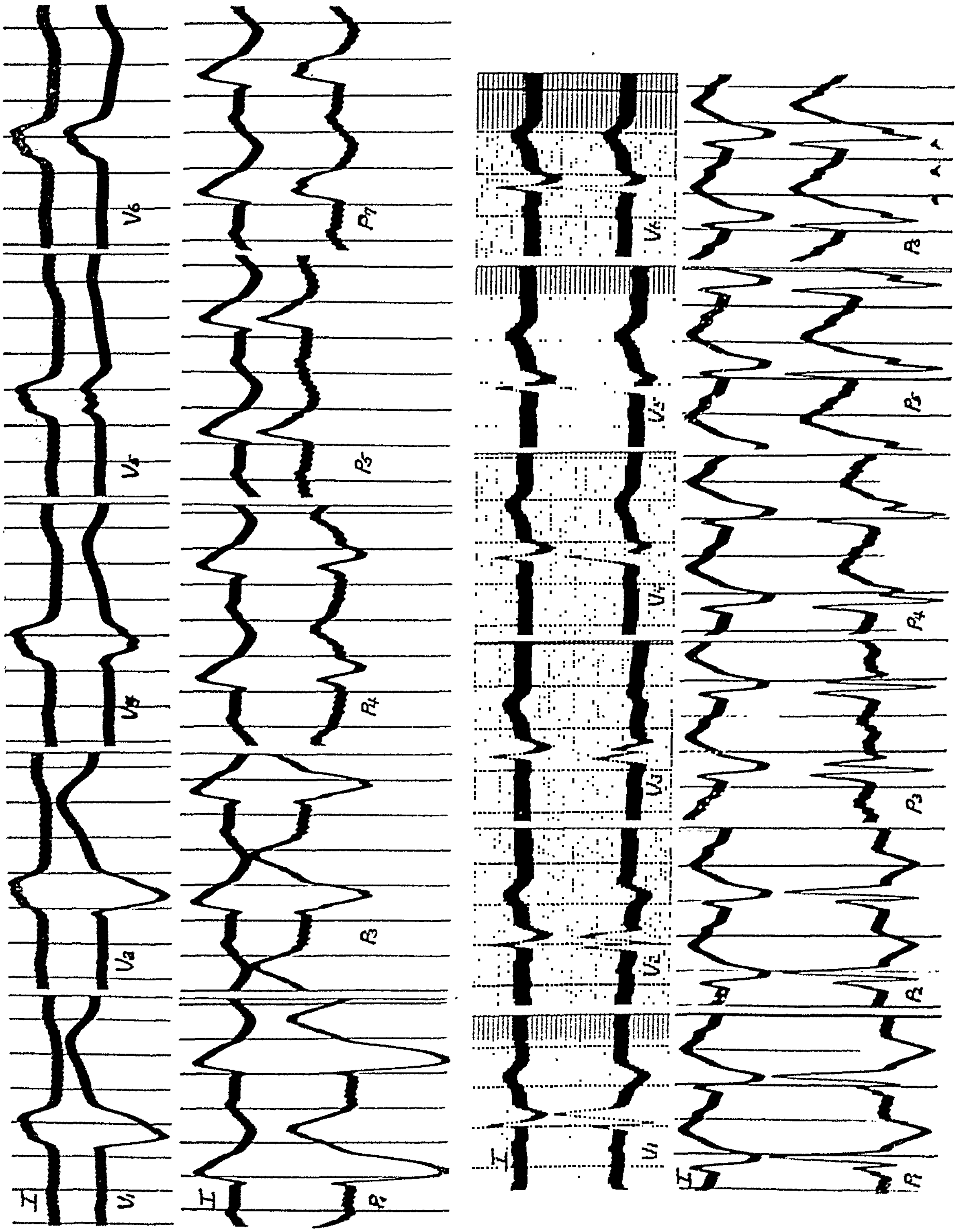


Fig. 5.—The precordial electrocardiogram in bundle branch block. (1) Human left branch block. (2) Canine left branch block. (3) Human right branch block. (4) Canine right branch block.

precordium show narrow R and broad notched S deflections, indicating early activation of the left ventricular surface. It is evident that, if precordial leads instead of limb leads had been used in the early studies of experimental and clinical bundle branch block, human left branch block could never have been mistaken for right branch block over a period of nearly twenty years. The confusion which prevailed over this long period arose because the dog's heart is almost always in the semivertical position, whereas, in patients with arteriosclerotic heart disease, the heart is usually in either the semihorizontal or the horizontal position. Since the relations between the surfaces of the two ventricles and the attachments of the extremities to the trunk are not constant in man, the differentiation of human right, from human left, bundle branch block, on the basis of the data furnished by limb leads alone, is sometimes impossible.

Comparison of Precordial and Direct Leads.—The similarities and differences between unipolar precordial leads and unipolar direct leads from the anterior surface of the heart can be appreciated only when these two kinds of leads are directly compared. In a number of experiments on dogs, we cut one of the branches of the His bundle under aseptic conditions, restored the chest, and allowed the animal to recover completely. Approximately one month after this operation, unipolar precordial leads were taken with the chest intact. The heart was then exposed by splitting the sternum and the potential variations of numerous points on its anterior surface were recorded.

The curves shown in Fig. 6 are from an experiment in which the right branch of the His bundle was cut twenty-six days before the electrocardiographic studies were made. Six of the precordial electrocardiograms are reproduced (P_1, P_3, P_4, P_5, P_6, and P_8). Below these are the records of the potential variations of three points on the right ventricle (points *4*, *5*, and *6*), one point near the interventricular sulcus (point *3*), and two points on the surface of the left ventricle (points *1* and *2*). Point *4* was on the conus, point *5* near the atrioventricular groove, point *6* in the central region, and points *2* and *1* on the left border above the apex.

The first three curves of the bottom row were obtained before the chest was opened by thrusting a sharp exploring electrode, insulated except at the extreme tip, through the chest wall on the right side of the precordium. The first curve was taken when the tip of the electrode was just beneath the skin, the second when it touched the heart and yielded a monophasic response, and the third when it was in the cavity of the right ventricle. The last three curves were obtained in the same way except that the sharp electrode was thrust through the chest wall at a point just inside the apex beat, consequently entering the cavity of the left ventricle. It will be noted that the cavity of this chamber was negative throughout the QRS interval. The potential variations of the

cavity of the right ventricle were not of the usual form inasmuch as the positivity of this chamber, due to the spread of the impulse through the septum from left to right, did not occur at the very beginning of the QRS interval as it ordinarily does. The R wave to which it gave rise is preceded, therefore, by a Q deflection.

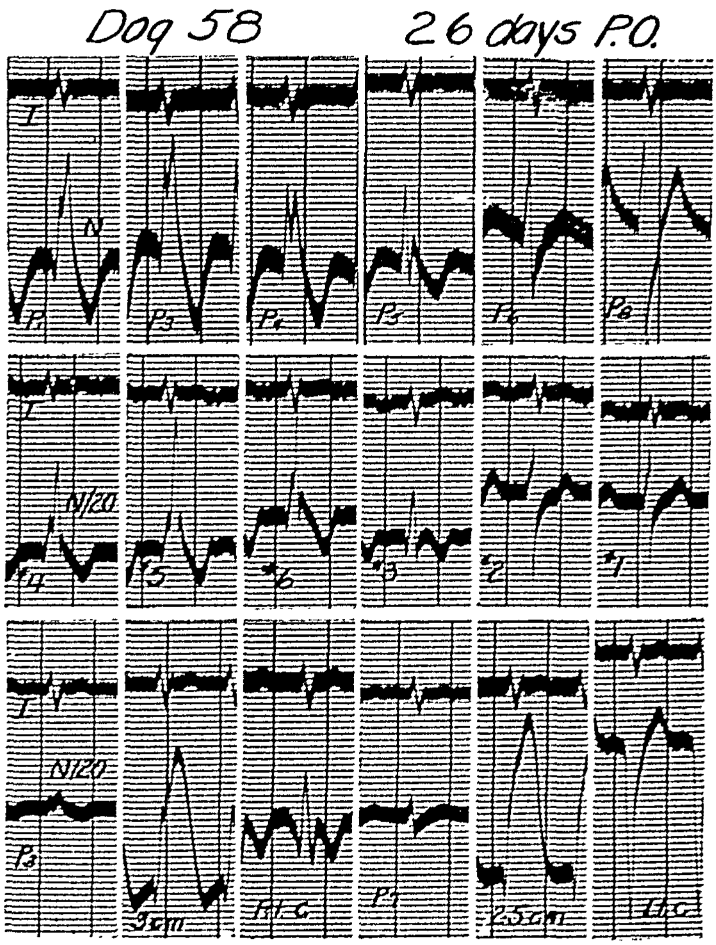


Fig. 6.—Precordial and direct leads in canine right branch block. (1) The precordial electrocardiogram. (2) Direct leads from three points on the right and three points on the left ventricle. (3) *Rt. C,* Potential variations of the cavity of the right ventricle. *Lt. C,* Potential variations of the cavity of the left ventricle.

The curves shown in Fig. 7 are from an experiment in which the left branch of the His bundle was cut twenty-seven days before the electrocardiographic study was made. Eight precordial electrocardiograms are reproduced. Below these are records of the potential variations of the cavity of the right ventricle (*12c*), three points on the right ventricle (*8, 3, 5*), three points on the left ventricle (*6, 1, 7*), and the cavity of the left ventricle (*13c*). Point *8* was near the atrioventricular groove, point *3* in the upper part of the central region, point *5* close to the trabeculated region, point *6* near the apex, and points *1* and *7* on the left border well above the apex. It will be noted that the cavity of the right ventricle was negative throughout the QRS interval while that of the left ventricle displayed initial positivity.

The similarity between the potential variations of the exposed surface of the right ventricle and the potential variations of the right side of the precordium, and between the potential variations of the surface of the left ventricle and those of the left side of the precordium in these two experiments requires no comment. We may point out, however, that the first peak of the bifid R waves often recorded over the delayed ventricle occurs when the cavity of that ventricle is positive, whereas the second peak, which marks the beginning of the intrinsic deflection, occurs when the cavity is negative. In those cases in which the peak of this broad R wave is not divided, the first peak is usually represented by a shoulder on its ascending limb.

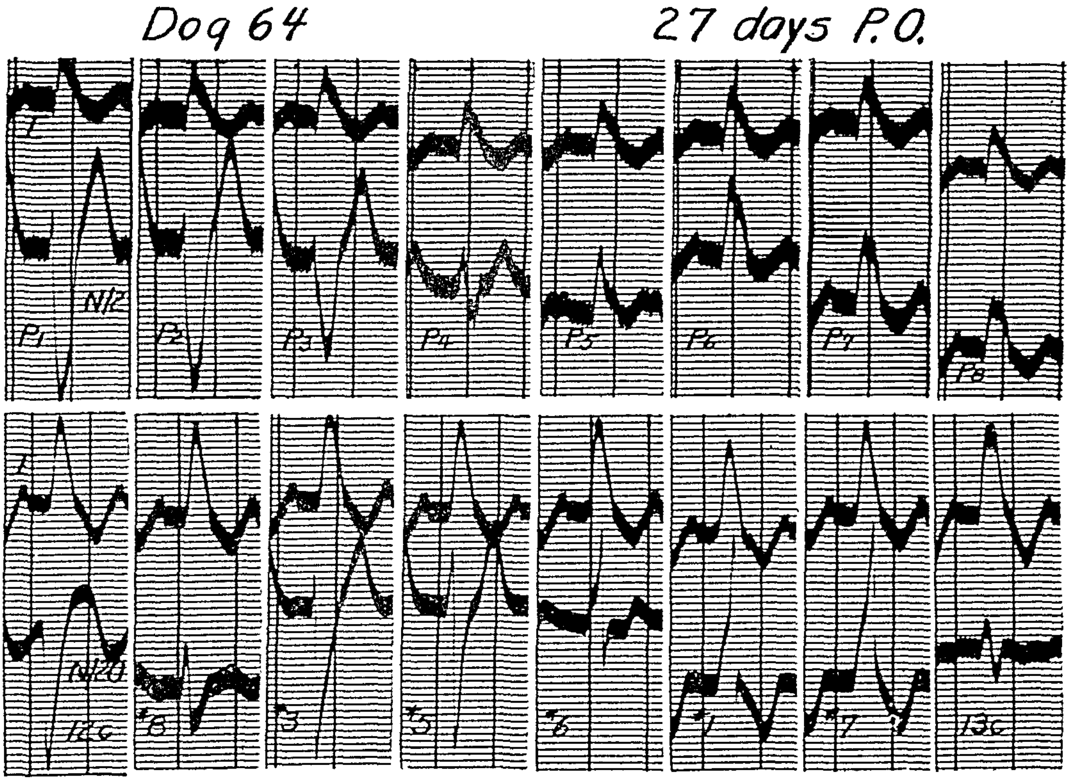


Fig. 7.—Precordial and direct leads in canine left branch block. (1) The precordial electrocardiogram. (2) The potential variations of three points (*8, 3, 5*) on the right, and three points (*6, 1, 7*) on the left ventricle. Potential variations of the cavity of the right (*12c*) and of the cavity of the left (*13c*) ventricle.

Human Bundle Branch Block.—There can be no reasonable doubt that, in man as in the dog, the potential variations of the right side of the precordium (Leads V_1 and V_2) ordinarily resemble the potential variations of the anterior surface of the right ventricle, while the potential variations of the left side of the precordium (Leads V_5 and V_6) ordinarily resemble the potential variations of the anterolateral surface of the left ventricle.

The electrocardiograms shown in Fig. 8 are those of a man who was examined both before and after he developed left bundle branch block. The tracings of March 28, 1940, display slight left axis deviation and flat T waves in Lead II; the QRS interval measures about 0.09 second.

On Dec. 9, 1940, left branch block was present. On this occasion, unipolar limb leads, unipolar precordial leads, and unipolar leads from the left infrascapular region were taken. The potential variations of the left arm (V_L) were similar to those of the left side of the precordium and the left infrascapular region, whereas the potential variations of the left leg were like those of the right side of the precordium in general outline. The heart was then in the horizontal position.

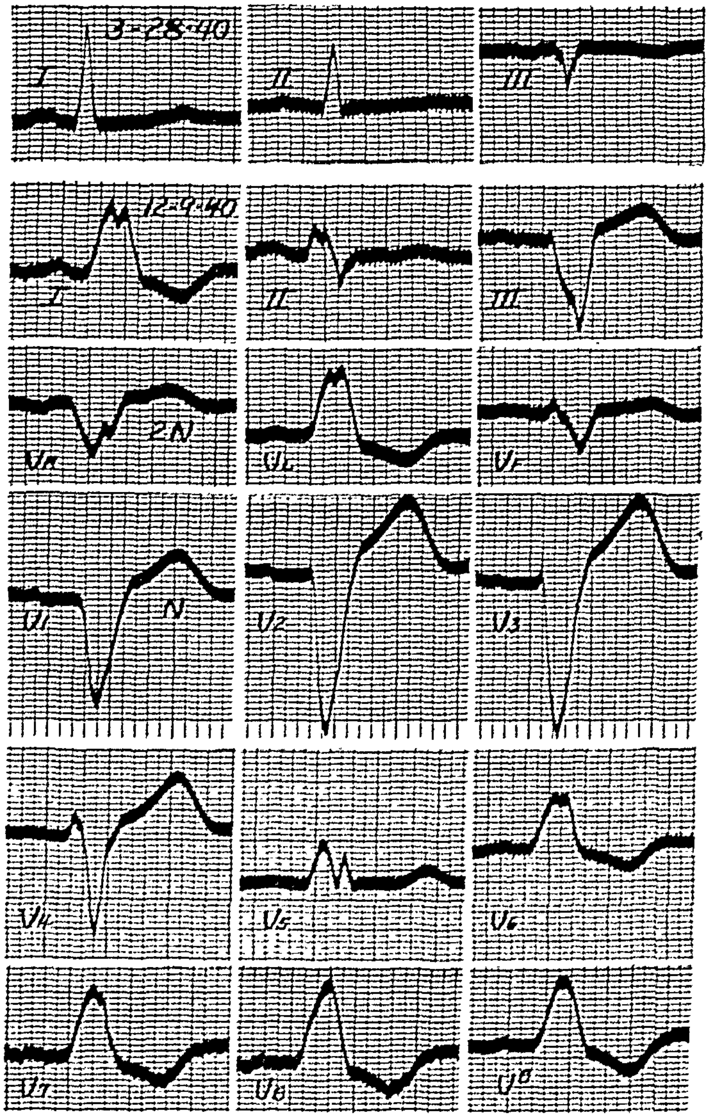


Fig. 8.—Left bundle branch block; heart in the horizontal position.

The electrocardiograms shown in Fig. 9 are those of a tall thin man who was examined for the first time on Feb. 3, 1937, when his electrocardiogram was normal. There was no deviation of the mean electrical axis at this time. On April 14, 1940, left bundle branch block was present and there were broad notched R deflections in Leads I and II and broad S deflections in Lead III. The precordial electrocardiograms of that date differ in no essential particular from those reproduced and

the heart was evidently in the semihorizontal position. On Nov. 27, 1940, and on Dec. 6, 1940, the ventricular complexes of the standard limb leads were of the concordant type. The unipolar leads taken on the latter date show that the potential variations of the left leg were like those of the left side of the precordium and the left infrascapular region. The potential variations of the left arm were small on both occasions. On these two days the heart was in the semivertical position.

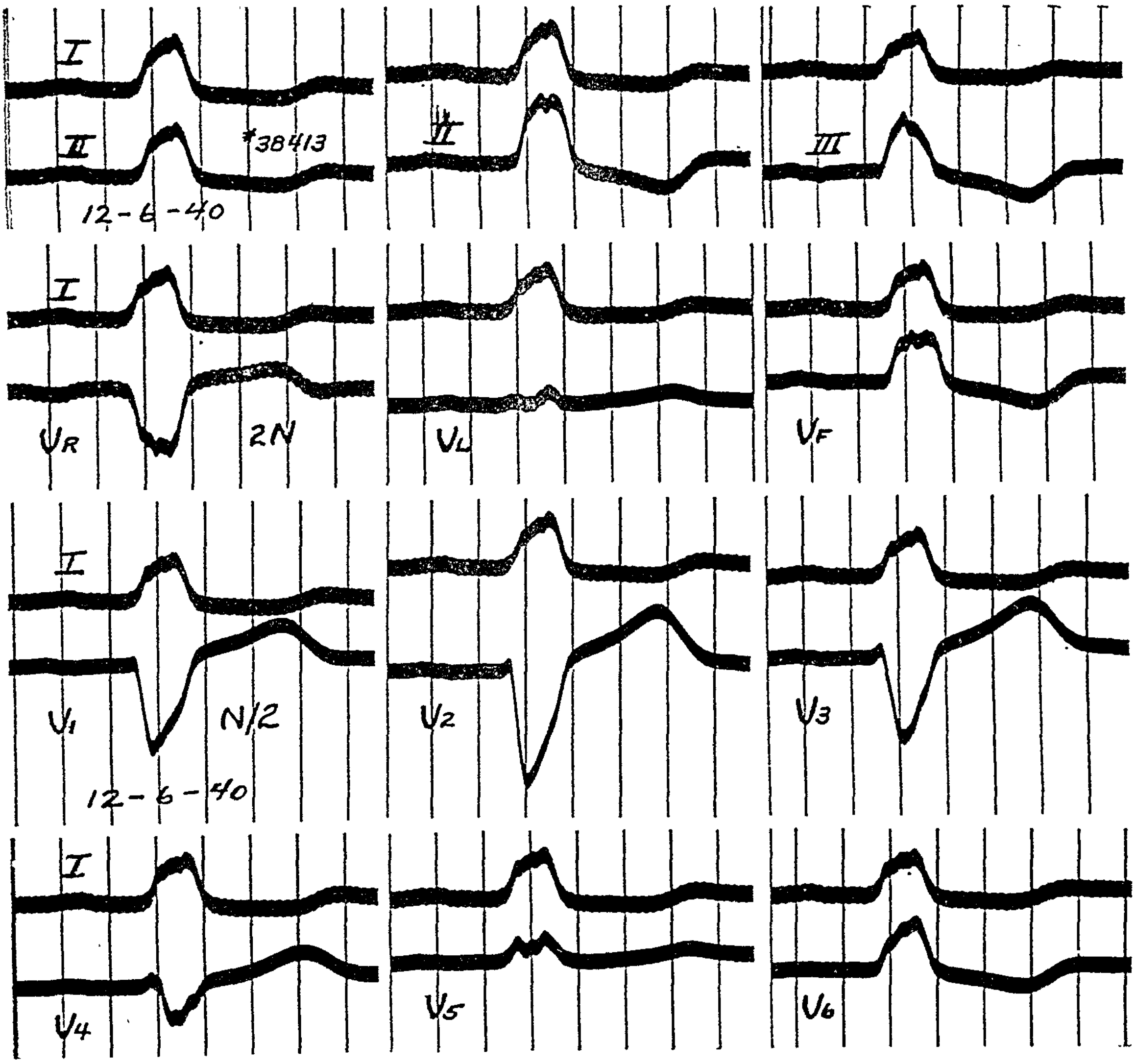


Fig. 9.—Left bundle branch block; heart in the semivertical position.

The patient whose electrocardiograms were reproduced in Fig. 10 was under observation from Feb. 26, 1941, until March 22, 1941. The ventricular complexes of the standard limb leads were quite variable in form. The curves taken on February 28 display discordant ventricular complexes of the kind ascribed to bundle branch block of the rare type. Those taken on March 14 show small bizarre QRS deflections in Lead I and diphasic QRS complexes with broad initial R waves in Leads II and III. In the tracings taken on Feb. 26, March 13, March 18, and March 26, the ventricular complexes are intermediate in form between the two types reproduced. Precordial electrocardiograms were taken on March

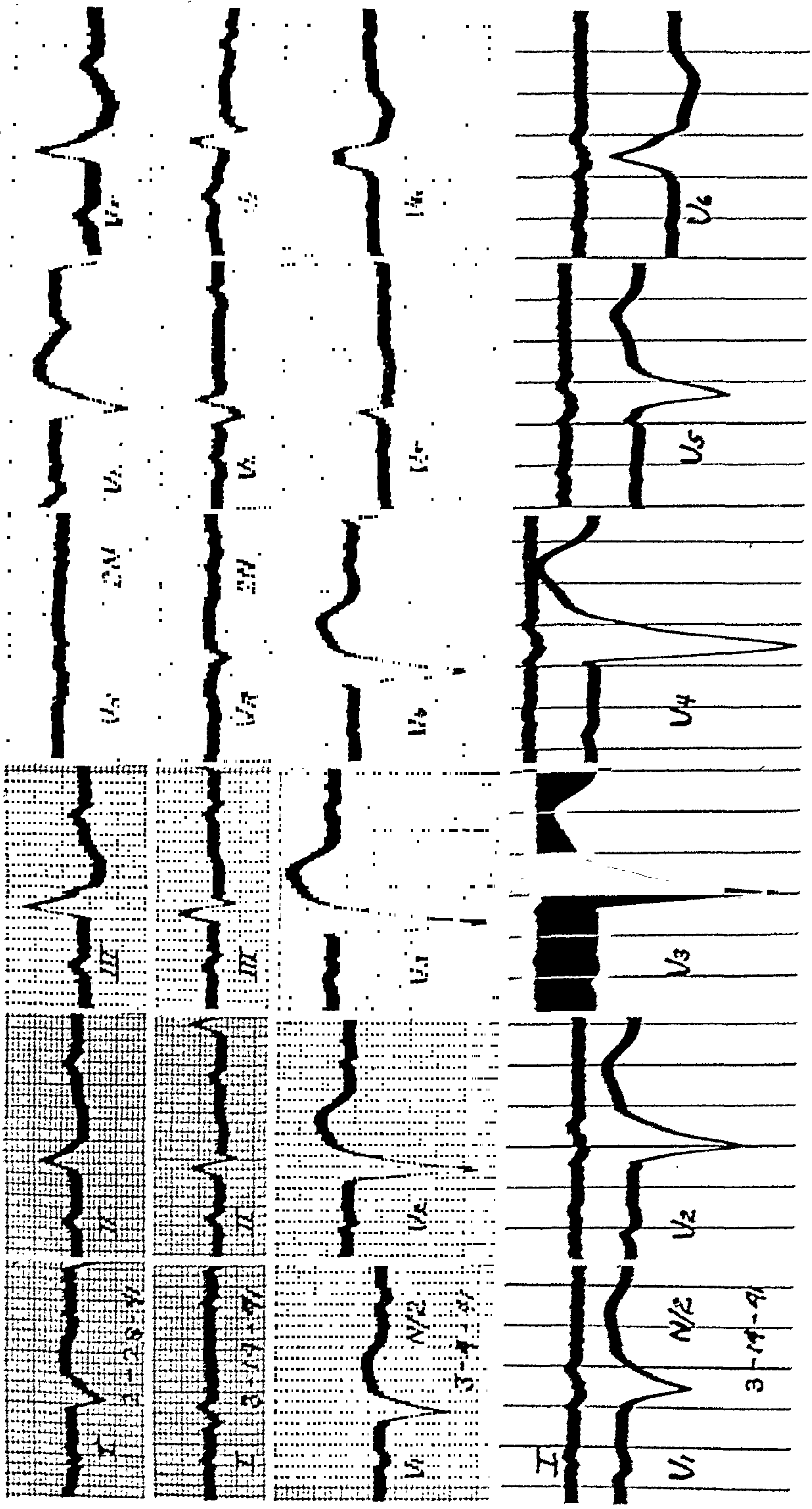


FIG. 10.—Left bundle branch block: heart in the vertical position. (From an article by Wilson.[8])

4 and on March 14, and the two sets of curves differ only as regards the form of the ventricular complexes of Lead V_5. Differences of this kind have no important significance. They are apparently due to variations in the position of the heart or to slight variations in the locations of the precordial points explored. The precordial electrocardiograms demonstrate beyond question that the conduction defect was in the left branch of the His bundle and not in the right.[15] When they are compared with the unipolar extremity curves taken on February 28, it is clear that the heart was then in the vertical position. On that date, the potential variations of the left arm were like those subsequently found on the right side of the precordium and the potential variations of the left leg like those found on the left side of the precordium. On March 14, the heart was in a somewhat different position. On that day, the potential variations of the left arm and of the left leg were apparently complicated mixtures of components transmitted from the surface of the right ventricle, and components derived from the surface of the left ventricle.

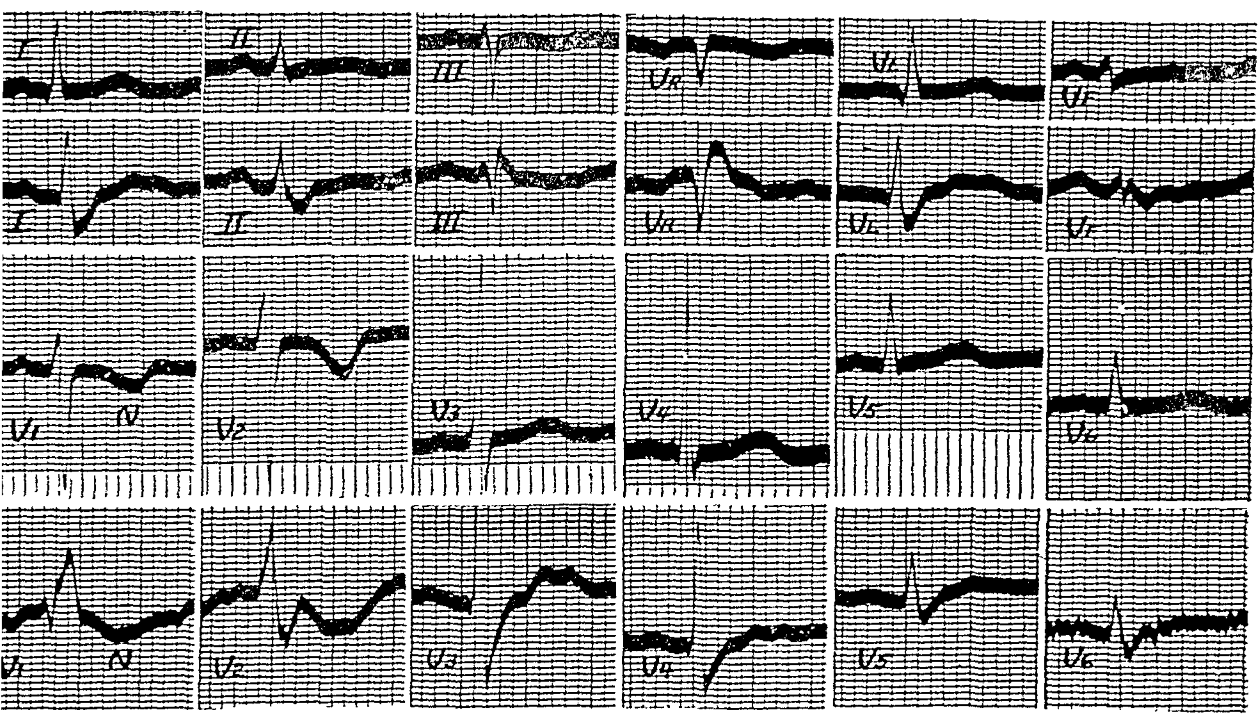


Fig. 11.—Right bundle branch block induced by quinidine; heart in the semihorizontal position.

The electrocardiograms reproduced in Fig. 11 are those of a young woman with ulcerative colitis who developed right bundle branch block on two different occasions after the administration of 0.4 Gm. of quinidine sulfate. Before the drug was given, slight left axis deviation was present, but, apart from inversion of the T waves in Lead V_2, both the standard and the precordial electrocardiogram were within normal limits. In both sets of curves, the ventricular complexes of Lead V_L resemble those of Leads V_5 and V_6, and the deflections of Lead V_F are

small. The heart was then in the semihorizontal position. It will be noted that the onset of right branch block produced more striking changes in the form of the ventricular complexes of Lead V_1 than in the form of those of Leads V_5 and V_6. In the latter, the R wave was slightly smaller and the S deflection deeper and broader after the block than before; in the former, the deep S originally present was replaced by a broad slurred R′ when the block developed. When the cardiac mechanism was normal, the transitional zone which yields complexes intermediate in form between those obtained from points farther to the left and those obtained from points farther to the right lay between precordial points *2* and *3*. When right branch block was present, it lay between points *1* and *2*; only the first precordial lead yielded ventricular complexes of the kind seen in direct leads from the surface of the right ventricle. On the second occasion on which right branch block was induced by quinidine, this apparent shift in the transitional zone did not occur.

The electrocardiograms reproduced in Fig. 12 represent right bundle branch block in a man whose heart was in the semivertical position. The precordial electrocardiogram displays the features usually associated with this conduction defect; the transitional zone lay between points *3* and *4*. In the standard limb leads the ventricular complexes are of the concordant type. The potential variations of the left leg were like those of the left side of the precordium and the potential variations of the left arm were very small.

The electrocardiograms reproduced in Fig. 13 are those of a man, aged 62 years, with arteriosclerotic heart disease. The ventricular complexes of the standard limb leads suggest that left branch block was present. It should be noted, however, that a Q and an S deflection are present in Lead I; both of these components are extremely rare in this lead in left branch block but common in right. The precordial electrocardiogram shows that the conduction defect was on the right side, but it is peculiar as regards the size of the R deflection in Leads V_5 and V_6. The small size of the R waves in these leads suggests that the block was complicated by some factor which diminished the magnitude of the forces produced by activation of the anterolateral wall of the left ventricle. Although no unipolar limb leads were taken, the form of the complexes of the standard limb leads shows that the potential variations of the left leg were like those of the left side of the precordium and the potential variations of the left arm like those of the right side of the precordium. The heart was, therefore, in the vertical position.

When the QRS interval measures 0.12 second or more, and the QRS complex in Lead I is monophasic and consists of a broad, slurred, flat-topped, or bifid R deflection, the precordial curves are, almost always, characteristic of left branch block. When the QRS interval measures 0.12 second or more, and the QRS complex in Lead I is biphasic or triphasic and ends with a broad, slurred or notched S deflection, the

precordial curves are, in the vast majority of cases, characteristic of right bundle branch block. The occasional exceptions to these general rules are due to a number of different causes. When the heart is in the vertical position, the limb leads may suggest that right branch block is

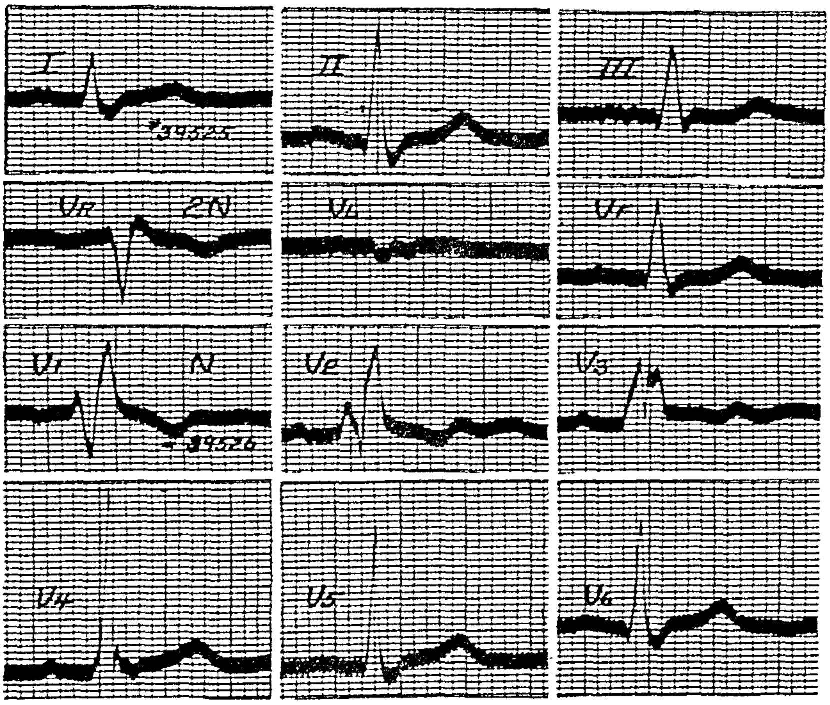


Fig. 12.—Right bundle branch block; heart in the semivertical position.

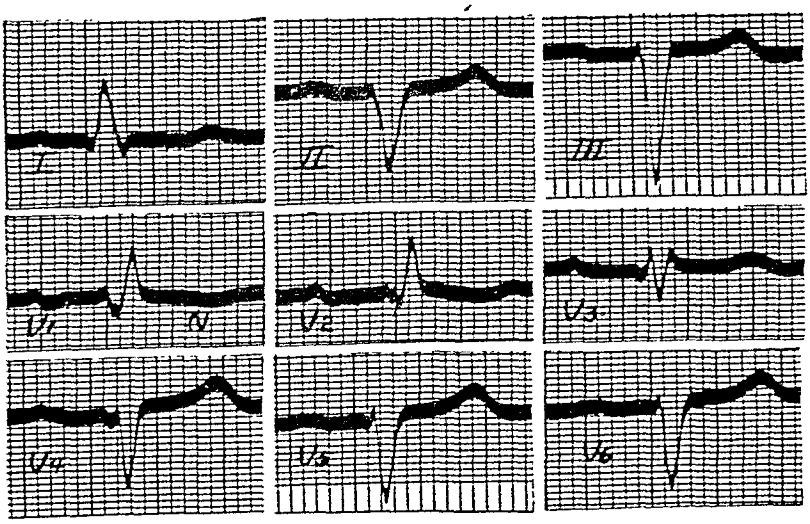


Fig. 13.—Right bundle branch block; heart in the vertical position. (From an article by Wilson.[15])

present when the precordial curves are characteristic of left branch block, and vice versa. In other instances, the prolongation of the QRS interval is due to a general depression of the conductivity of the Purkinje tissue or to local lesions involving the subendocardial Purkinje network over a considerable area ("arborization block").[16] The latter is seen most often in association with extensive myocardial infarction.

When the QRS interval measures 0.12 second or more, and the precordial electrocardiogram shows some but not all of the features typical

of right or of left branch block, the conduction defect cannot be located with certainty. Sometimes this situation arises because this defect is associated with lesions which modify its effects upon the electrocardiogram. Sometimes it depends upon peculiarities in the extent or location of the transitional zone, which separates the parts of the precordium that display potential variations like those of the anterior surface of the right ventricle, from the parts of the precordium that display potential variations like those of the anterolateral surface of the left ventricle. This may be so far to the left or so far to the right that all of the six standard precordial leads yield ventricular complexes of the same type. When this happens, it is desirable to take additional unipolar leads so arranged as to cross this zone. It is still impossible to say why the transitional zone is so variable in width and location. Finally, it should be emphasized that in many cases of bundle branch block there is no obvious relation between the form of the ventricular complexes of the precordial leads and the form of the ventricular complexes of the limb leads. In these cases the position of the heart must be classed as indeterminate.

When the QRS interval is abnormally long but measures distinctly less than 0.12 second, the precordial curves are seldom characteristic of complete bundle branch block. In rare instances they are typical of right branch block even though the QRS interval of the limb leads is not much greater than 0.10. In most of the cases of this kind that we have seen we suspected that the right ventricle was greatly hypertrophied, and it is possible that this condition was in part responsible for the form of the precordial electrocardiogram.

Unipolar precordial leads make it possible to diagnose incomplete right bundle branch block in many cases in which it cannot be recognized by other means. Except under special circumstances, the diagnosis of incomplete left branch block is still very difficult to make with certainty.

The electrocardiograms reproduced in Figs. 14 and 15 represent the alternation of complete with incomplete right branch block. The first ventricular complex of each pair represents complete, and the second incomplete, block. It will be noted that as regards their earliest components the paired complexes are identical in all leads. In the case of the limb leads and the leads from the left side of the precordium (V_5 and V_6), the sole difference lies in the width of the final QRS component and the size of the T deflection. In the leads from the right side of the precordium (V_1 and V_2), from the tip of the ensiform process (V_E), and from the right nipple line, the difference is much greater; the large final R′ deflection of the first complex is very much smaller (V_1 and V_E) or embryonic* in the second (V_2). The presence of such

*This term is used to indicate that the peak of this deflection does not rise above the level of the trace at the beginning of the QRS interval.

small or embryonic R′ deflections, in addition to an initial R wave in the leads from the right side of the precordium, strongly suggests that incomplete right branch block is present, particularly when the QRS interval is slightly increased and there is a broad S wave in Lead I and in the leads from the left side of the precordium. It is advisable to take precordial leads whenever the QRS complex of Lead I is of this kind.

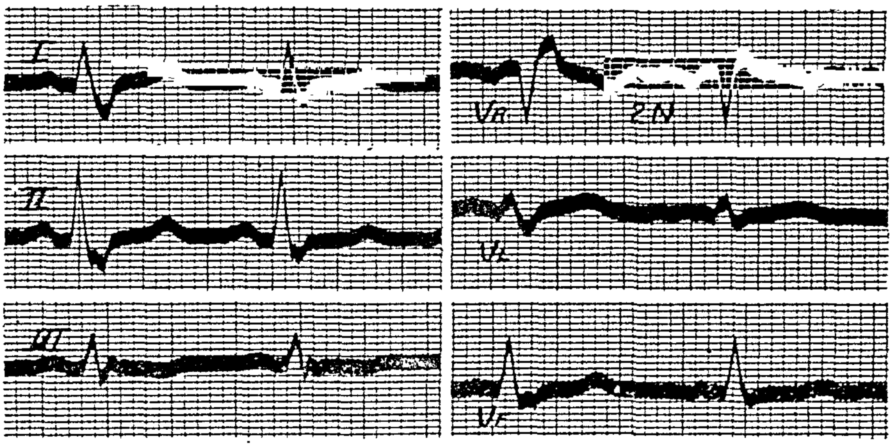


Fig. 14.—Complete and incomplete right bundle branch block; standard and unipolar limb leads.

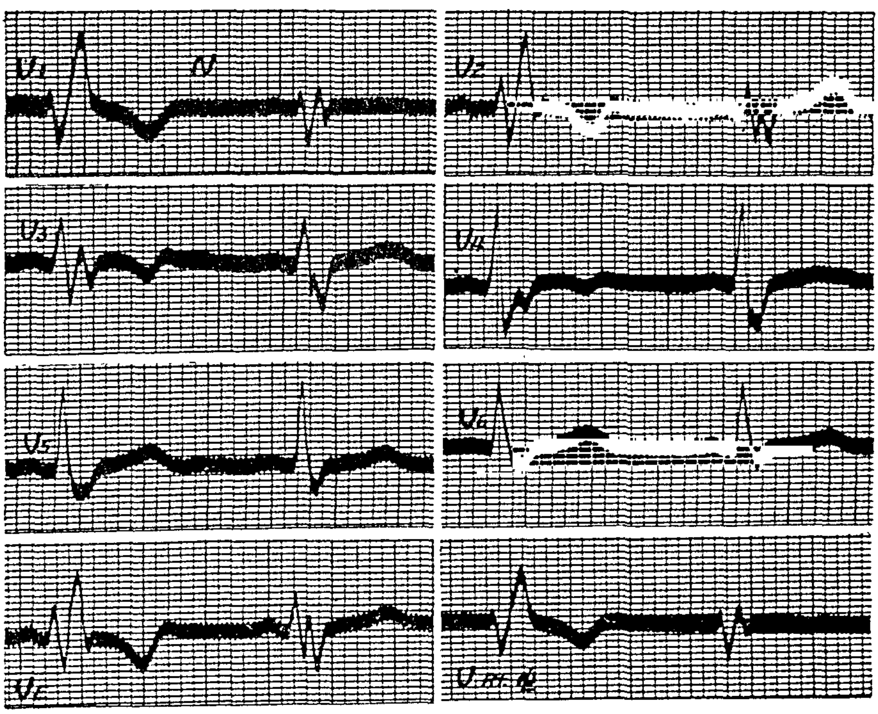


Fig. 15.—Complete and incomplete right branch block; precordial leads.

In incomplete left bundle branch block, the precordial electrocardiogram resembles that seen in preponderant hypertrophy of the left ventricle and the two conditions frequently coexist. The presence of a Q deflection in the leads from the left side of the precordium excludes the former, but the absence of this deflection does not differentiate one from the other.

Transient Branch Block.—In the vast majority of the cases of human bundle branch block, there is no way of knowing whether all the electrocardiographic abnormalities present are due to the conduction defect or whether some of them are the result of the other lesions which are almost always present. Cases in which the electrocardiogram is normal after branch block disappears, or immediately before it develops, are, therefore, of unusual interest. In such cases the effects produced by the block are uncomplicated by other factors.

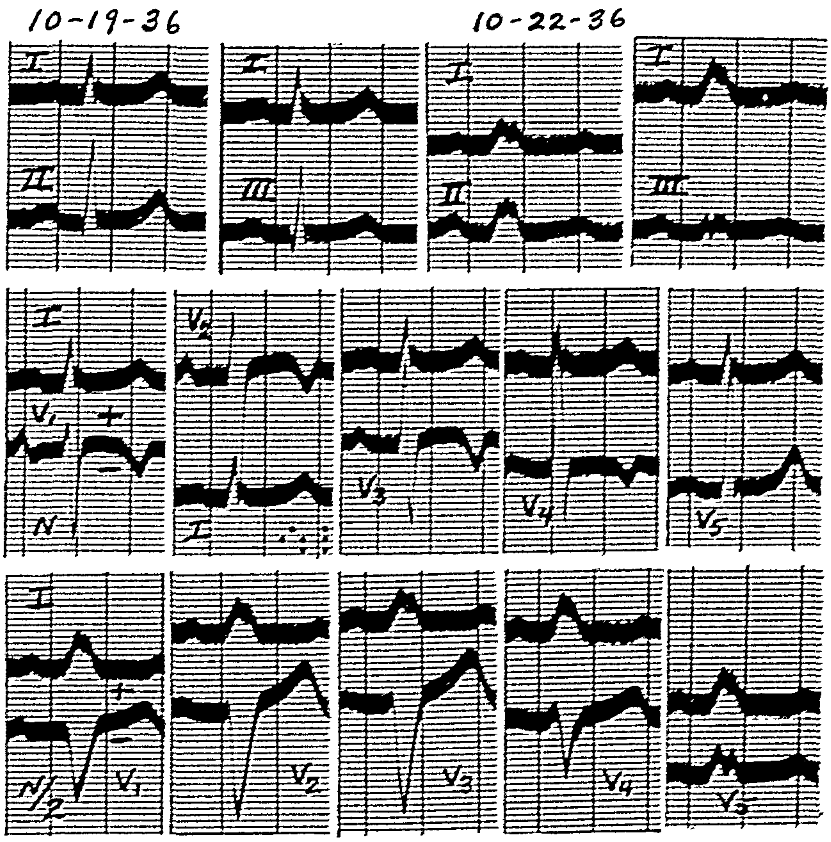


Fig. 16.—Transient left branch block.

The electrocardiograms reproduced in Fig. 16 are those of a woman, aged 55 years, who had symptoms suggesting hyperthyroidism. She was under observation from Oct. 13, 1936, until Nov. 3, 1936. Left branch block was present when the patient was seen for the first time, but, on October 19, the standard extremity curves were normal. At this time the precordial curves were normal as regards the QRS complexes, but the T waves were sharply inverted in Leads V_1, V_2, V_3, and V_4. This case conforms to the rule that abnormalities which are confined to the leads from the right side of the precordium are not accompanied by similar abnormalities in the limb leads. It illustrates the value of precordial leads in detecting lesions which produce electrocardiographic disturbances of this kind. On October 22, the branch block was again present. In the standard leads the broad notched QRS deflections were of

low voltage and of the concordant type. In the precordial leads the voltage of the chief QRS deflection was so large that, in order to record it properly, it was necessary to reduce the string galvanometer to one-half the normal sensitivity. It will be noted that the conduction defect greatly reduced the size of the R waves in the leads from the right side of the precordium, abolished the inversion of the T waves previously present in these leads, and shifted the transitional zone to the left. In the leads from the left side of the precordium (V_5 and V_6), it gave rise to monophasic QRS complexes consisting of broad, bifid R deflections. It is evident that the heart was in the semivertical position.

The electrocardiograms reproduced in Fig. 17 are those of a woman, aged 24 years, with rheumatic heart disease. She was under observation from Nov. 16, 1938, until April 25, 1939. When she was first seen, the electrocardiogram displayed rather large P deflections, but was not definitely outside normal limits. On April 5, the P-R interval measured 0.32 second, and right branch block was present. On April 14, the electrocardiogram was normal and precordial leads were taken. On April 25, right branch block was again present and the precordial leads were repeated. It will be noted that the block gave rise to a large final R′ deflection in Leads V_1 and V_2, inverted or flattened the T waves in the first four precordial leads, made the R deflections somewhat smaller in the leads from the left side of the precordium, and produced broad S waves in Leads V_5 and V_6.

Ventricular Hypertrophy.—Preponderant hypertrophy of the left ventricle increases the thickness and the bulk of its walls. When uncomplicated, its chief effect is, therefore, to exaggerate the normal difference in this respect between this chamber and its fellow. It is not surprising, then, that in left ventricular hypertrophy, unipolar precordial leads yield curves which, in their broader aspects, are not unlike those obtained when the heart is normal. The chief differences are these: In left ventricular hypertrophy the voltage of the chief deflection of the QRS group is on the average much greater than normal, and the QRS interval is increased to 0.10 or even 0.11 second. In the leads from the right side of the precordium the R deflections are, on the average, much smaller than normal and may be absent.[17] The transitional zone is, as a rule, much displaced to the left. In the leads from the left side of the precordium, R, and often Q as well, is abnormally large; the peak of R occurs abnormally late in the QRS interval; and the T deflections are inverted.

By increasing the bulk and thickness of its walls, preponderant hypertrophy of the right ventricle tends to abolish or reverse the normal difference between it and the left. In high-grade right ventricular hypertrophy, the precordial curves are, as regards their broader aspects, somewhat like those obtained in right branch block, but the QRS inter-

val is not increased and the QRS deflections are not ordinarily broad, slurred, or notched. On the average, the voltage of the chief QRS deflection is above normal although not as large as in left ventricular hypertrophy.[17] In the leads from the right side of the precordium,

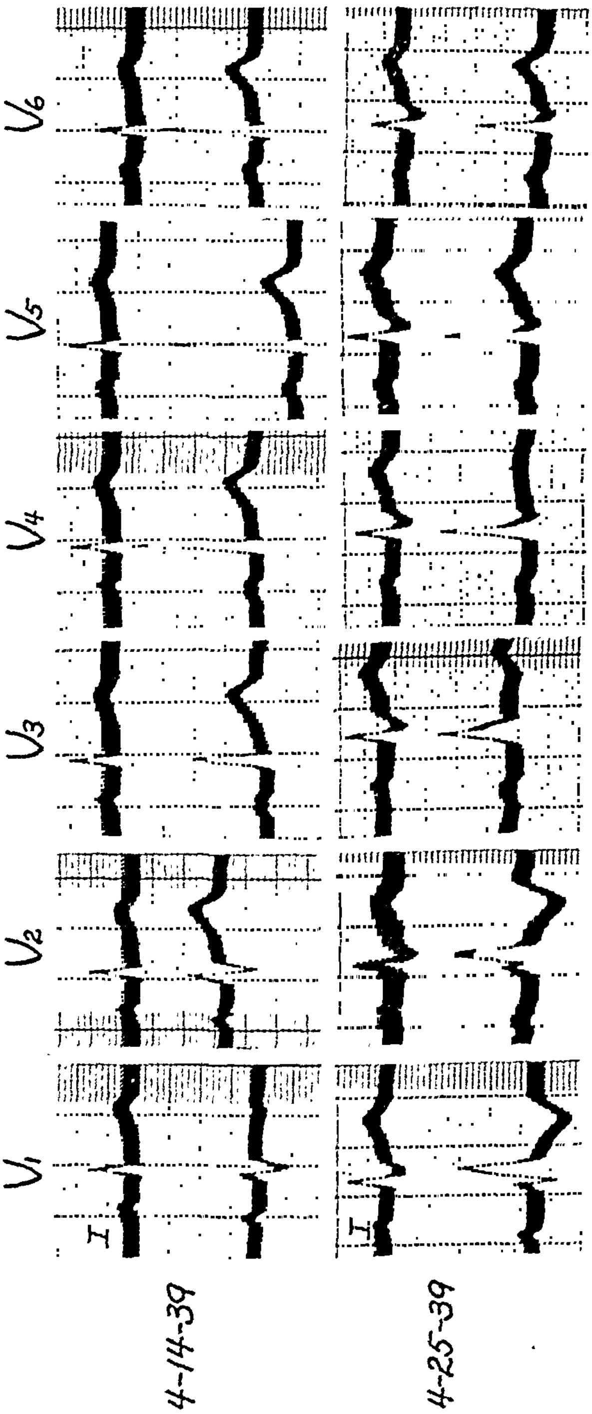


Fig. 17.—Transient right branch block.

the R wave is very large, Q is frequently present, S is usually absent, and the T deflections are commonly inverted. In some instances a small initial upward deflection precedes the first downward deflection of the

QRS group, but we suspect that the presence of such a summit may be due to incomplete right branch block. In the leads from the left side of the precordium the R deflections are abnormally small and the S deflections abnormally large. In other words, the precordial curves are opposite in type to those obtained when the heart is normal.

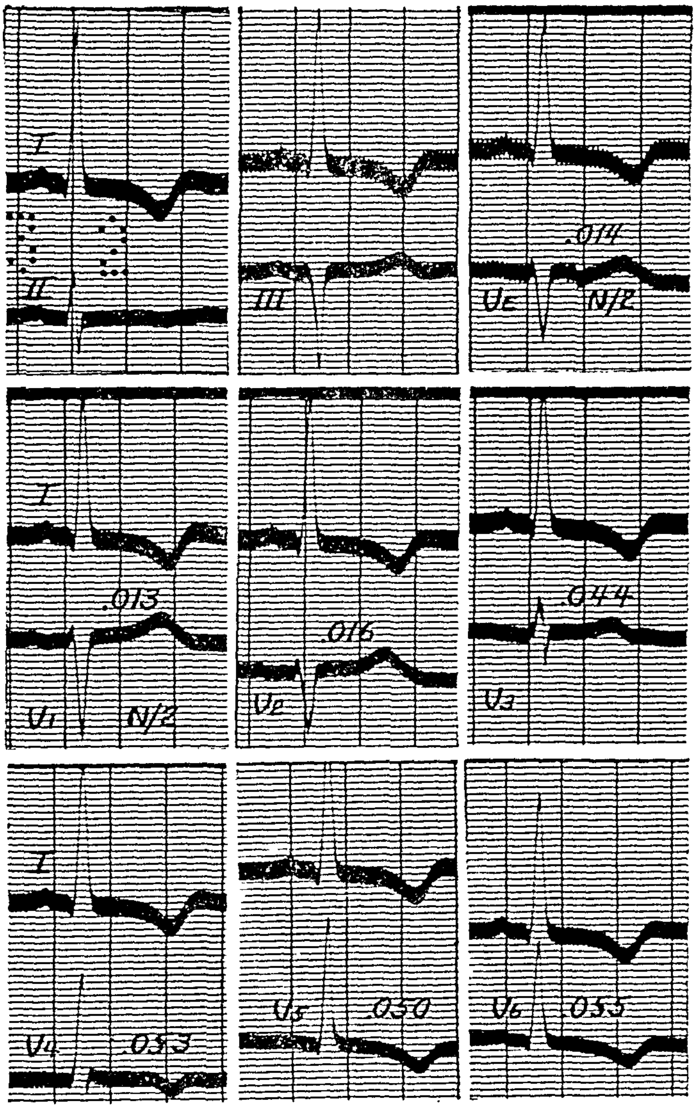


Fig. 18.—Left ventricular hypertrophy; heart in the horizontal or semihorizontal position.

In left ventricular hypertrophy the position of the heart has the same effect upon the mean electrical axis of QRS as in normal subjects. The electrocardiograms reproduced in Fig. 18 are those of a man, aged 54 years, with hypertensive heart disease. The standard extremity curves display left axis deviation, a QRS interval measuring approximately 0.10 second, and prominent Q waves, abnormally large R deflections, and inverted T waves in Lead I. The precordial curves, which were taken with the galvanometer at one-half the normal sensitivity, are characteristic of left ventricular hypertrophy. Although no unipolar limb leads were taken, it is clear that the heart was in the horizontal or semihorizontal position.

The electrocardiograms reproduced in Fig. 19 are those of a woman, aged 50 years, with hypertensive heart disease. No axis deviation is present, but the R deflections are abnormally tall and the T waves inverted in all of the standard limb leads. The QRS interval is slightly increased. The precordial curves, which were taken with the galvanometer at one-half the normal sensitivity, are characteristic of left ventricular hypertrophy. The potential variations of the left leg were like those of the left side of the precordium and the potential variations of the left arm were small. The heart was in the semivertical position.

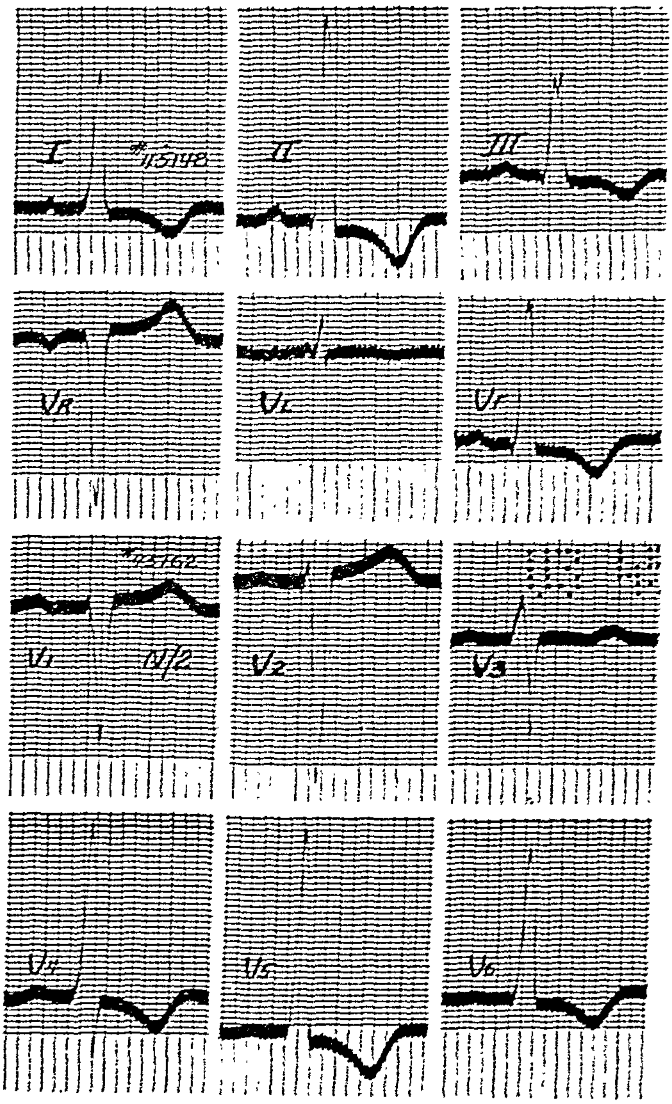


Fig. 19.—Left ventricular hypertrophy; heart in the semivertical position.

The electrocardiograms reproduced in Fig. 20 are those of a young man, aged 16 years, with rheumatic heart disease, aortic stenosis and regurgitation and probably mitral stenosis, and an enormously enlarged heart. Right axis deviation is present, the T deflections are inverted in Leads II and III, the P-R interval is increased, and the P deflections

are large and deformed. Seven precordial leads were taken, the last, marked V_7, from the posterior axillary line at the level of the apex, which was not far inside this point. The precordial curves, which were taken with the galvanometer at one-half the normal sensitivity, are characteristic of left ventricular hypertrophy. Although unipolar limb leads were not taken, it is evident the potential variations of the left leg were like those of the left side of the precordium and the potential variations of the left arm like those on the right side of the precordium. The heart was, therefore, in the vertical position.

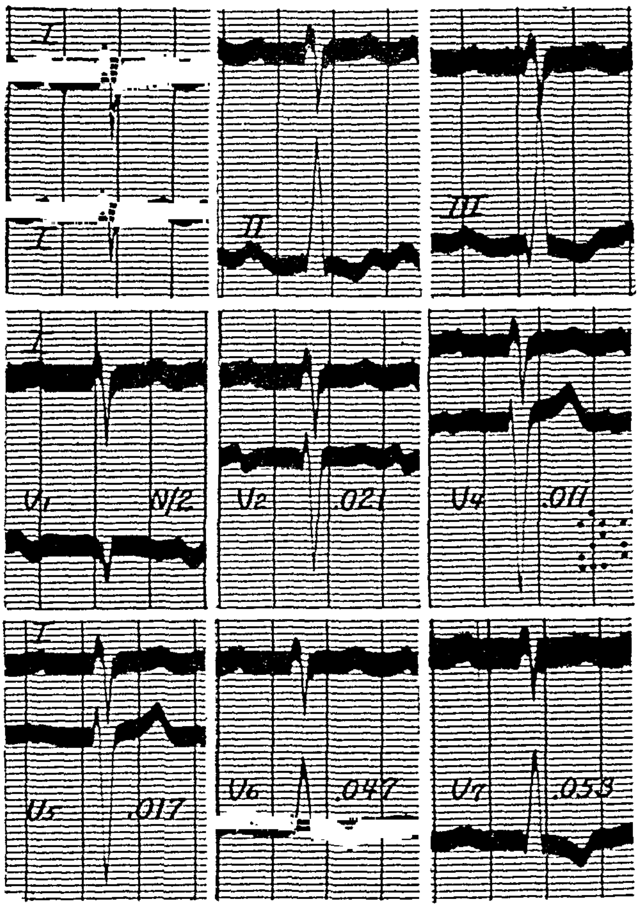


Fig. 20.—Left ventricular hypertrophy; heart in the vertical position. (From an article by Wilson, Johnston, Cotrim, and Rosenbaum.[13])

The electrocardiograms of two patients with right ventricular hypertrophy are reproduced in Fig. 21. The curves of the upper set are those of a woman, aged 34 years, who had pulmonary hypertension of unknown origin. The limb leads display conspicuous right axis deviation. The precordial curves are characteristic of right ventricular hypertrophy; tall R waves, prominent Q waves, and inverted T waves are present in Lead V_1, and small R and deep S waves in Leads V_5 and V_6. The potential variations of the left arm were like the potential variations of the left side of the precordium, and the potential variations of the left leg resembled those of the right side. The heart was in the horizontal position. The curves of the second set are those of a

man, aged 40 years, with mitral stenosis and aortic insufficiency. The precordial curves are characteristic of right ventricular hypertrophy. Large S waves and small R waves are present in all of the standard

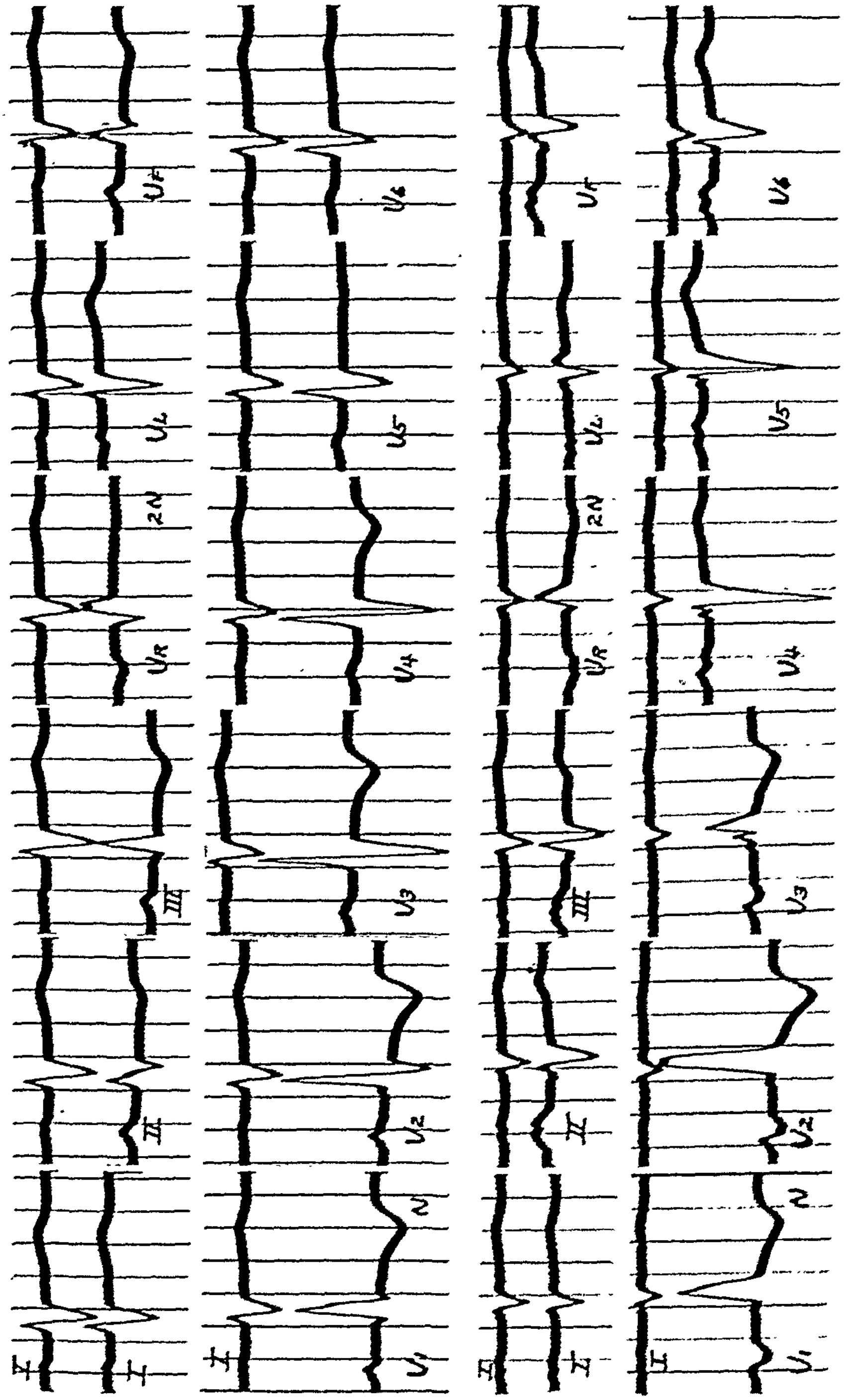


Fig. 21.—Right ventricular hypertrophy. (1) Heart in the horizontal position. (2) Heart in the semivertical position.

limb leads. Here the ventricular complexes of the unipolar leg lead are like those of Leads V_5 and V_6; the complexes of the right arm lead are like those of Lead V_1, and the complexes of the left arm lead apparently represent a mixture of the potential variations of the other two ex-

tremities. In this case the heart was apparently in the semivertical position.

When the heart is greatly enlarged, it is ordinarily in the horizontal or semihorizontal position. In either case, left ventricular hypertrophy produces left, and right ventricular hypertrophy produces right, axis deviation. When the heart is in the semivertical position, left ventricular hypertrophy produces abnormally tall R waves and, usually, inverted T waves, and right ventricular hypertrophy produces large S waves in all of the standard limb leads. When the heart is in the vertical position, left ventricular hypertrophy produces right, and right ventricular hypertrophy should produce left, axis deviation, although we have not as yet seen the latter occur.

The precordial curves of left ventricular hypertrophy are distinguished from those of left bundle branch block by the absence of slurred or bifid R waves and the great frequency of Q deflections in the leads from the left side of the precordium. In left branch block, the presence of Q in these leads suggests that the diagnosis is wrong or that septal lesions which prevent initial positivity of the left ventricular cavity are present. The QRS interval is almost always less than 0.12 second in hypertrophy, whereas, in block, it equals or exceeds this figure.

The precordial curves of right ventricular hypertrophy are distinguished from those of right bundle branch block by the absence of double or bifid R waves in the leads from the right side of the precordium, by the small size of the R waves in the leads from the left side of the precordium, and by the absence of a greatly increased QRS interval.

It must be admitted, however, that cases are frequently encountered in which it is impossible to say with certainty whether the electrocardiographic changes are due to hypertrophy alone or to hypertrophy plus incomplete bundle branch block.

Myocardial Infarction.—The character of the potential variations at the epicardial surface of an infarct depends upon the stage of infarction and upon whether the whole thickness of the ventricular wall or only the subendocardial layers of muscle are involved. Immediately after ligation of the anterior descending coronary artery or one of its branches in experiments upon the dog's heart, direct leads from the region supplied by the vessel occluded display pronounced upward displacement of the RS-T junction, which persists for many hours but disappears when the muscle affected dies or recovers.[18] This RS-T displacement is accompanied by a corresponding reduction in the voltage of the intrinsic deflection. When the whole thickness of the ventricular wall is involved and the infarcted muscle is already dead or incapable of responding to the excitatory impulse, the potential variations of the part of the ventricular cavity adjacent to the infarct are faithfully transmitted to its epicardial surface. Since the ventricular cavities

are normally negative throughout the QRS interval, direct leads from the central part of the infarct then yield QRS complexes which consist of a monophasic downward deflection (QS deflection). In many cases, some fraction of the muscle in this region remains alive and gives rise to an embryonic R wave which produces a notch on the descending or ascending limb of the single QRS component. When the subendocardial layers of muscle are for the most part dead or incapable of responding to the cardiac impulse, and the outer layers of muscle are relatively normal, the embryonic R rises above the base line and becomes a true R deflection. The QRS complex then consists of an abnormally large Q followed by a small R and often by an S deflection also. Since infarcts of the left ventricular wall are usually more extensive on the endocardial than on the epicardial side, QRS complexes of this kind are commonly seen in direct leads from the marginal parts of the infarcted area.[19] These same zones also yield deep, sharply inverted T deflections due to an increase in the duration of the excited state at the epicardial surface. In the dog, the T-wave changes develop some hours after infarction begins, and ordinarily disappear almost completely within twenty-four hours or less. In man, they commonly last for some weeks or months.

The potential variations of the epicardial surface of the infarcted region are transmitted to the adjacent parts of the body. When the anterior wall of the left ventricle is involved, they are transmitted to the precordium; if the anterolateral wall is involved, they are also transmitted to the left arm. If the posterior wall is infarcted, they are usually transmitted to the ventricular levels of the esophagus, to the back, and to the left leg. The potential variations of points at some distance from the heart but on the same side of it as the infarcted region are, of course, a mixture of components derived from the epicardial surface of the infarct, from regions adjacent to it, and from other parts of the ventricular surface. It is only when the infarct is large that characteristic curves are obtained by leading from regions distant from it. The potential variations of parts of the body on the side of the heart opposite the one involved, as regards their general character, are the inverse of those that occur at the surface of the infarct.

The diagnosis of myocardial infarction can be made with certainty from the electrocardiogram alone only when characteristic changes in the QRS complex occur in association with RS-T displacement or typical changes in the T deflections. Changes in the QRS complex have more diagnostic value than displacement or changes in the T waves when only electrocardiographic data are available, but they are not conclusive. When clinical data are available and are strongly suggestive of infarction, and serial curves are taken, the opposite is true because of the relatively rapid, progressive changes which the T complex undergoes. Similar changes may occur in pericarditis, but usually this can be ruled out on clinical grounds.

From the electrocardiographic standpoint, there are many types of infarcts which differ one from another as regards the character of the electrocardiographic changes and the leads in which they occur. Whether some of these varieties are determined by the position of the heart rather than the location and extent of the infarcted region, only the future can decide.

T-Wave Changes Only.—The electrocardiograms reproduced in Fig. 22 are those of a physician, aged 67 years, who was first seen on Aug. 7, 1934. At that time, the standard limb leads showed a considerable shift of the electrical axis to the left, but no other notable features. Myocardial infarction occurred early in March, 1940. Six weeks later (April 25, 1940) there was sharp inversion of the T deflections in all of the precordial curves although the limb leads showed no significant changes. After eight months, all electrocardiographic evidence of infarction had completely disappeared. The patient made an uneventful recovery. We have seen no instance of serious cardiac impairment following anterior infarction which produced no electrocardiographic abnormalities other than sharp inversion of the T waves.

Transient QRS Changes.—The electrocardiograms reproduced in Fig. 23 are those of a man who began to have symptoms typical of coronary thrombosis at 6:40 P.M., on Oct. 6, 1936, while he was under treatment for prostatic hypertrophy. On the following day, the standard electrocardiogram showed extremely small QRS deflections and flat T waves in Lead I. In the precordial leads there was a progressive diminution in the size of R as the exploring electrode was moved from the first to the fourth position, and this deflection was abnormally small in Leads V_5 and V_6. A month later, the QRS deflections were normal, but there was sharp inversion of the T waves in all of the limb leads and in the last four precordial leads. The patient's recovery was complete and uninterrupted.

It is apparent that, in this instance, the infarcted muscle was, for a time, incapable of responding to the excitatory impulse, but it was not dead and subsequently recovered its excitability. Very pronounced alterations in the QRS complex of the kind observed in this case seldom disappear completely, but they often undergo a very slow and much less pronounced retrogression. Very often, clear-cut and characteristic deformities of this complex and, much more rarely, residual changes in the T waves are still present years after the cardiac accident. An instance of this kind is illustrated in Fig. 24. The patient developed myocardial infarction in May, 1934, when he was 23 years old. The electrocardiograms taken at that time are not very different from those reproduced, which were made seven years later. When last seen, this young man was working and was free of symptoms. Note that the ventricular complexes of the unipolar left arm lead are like those of Lead V_5.

Persistent RS-T Displacement.—The electrocardiograms reproduced in Fig. 25 are those of a man, aged 73 years, who began to have anginal pain late in May, 1941, and developed myocardial infarction on June 11 of that year. Very pronounced RS-T displacement of the kind commonly seen in very recent anterior infarction was still present on Nov. 7,

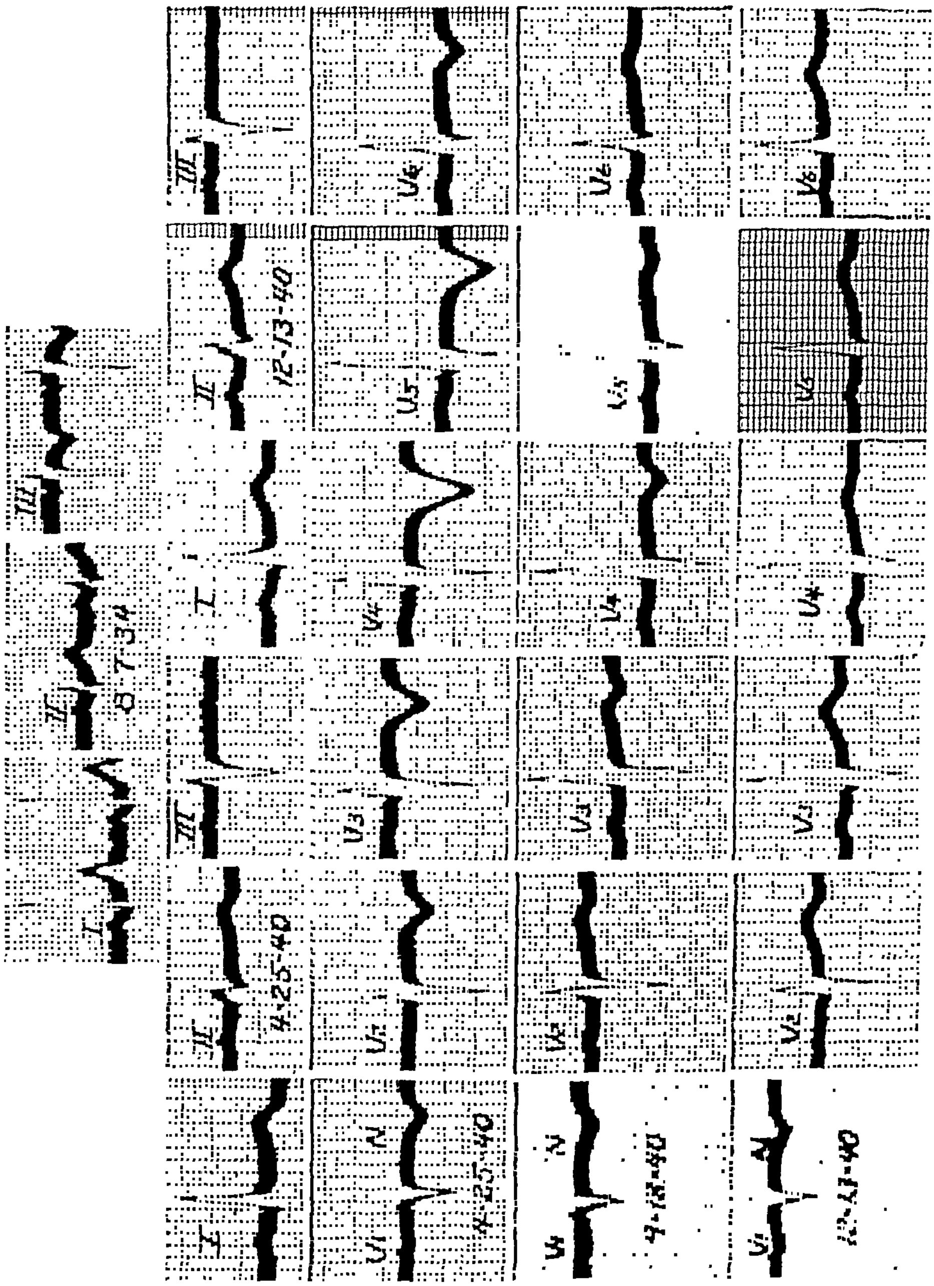


Fig. 22.—Anterior myocardial infarction; changes in the T waves only.

1941, when the first electrocardiogram was taken, and remained essentially unchanged on April 20, 1942. The patient developed congestive cardiac failure but had chest pain only during the earliest stage of his illness. Complete healing of the infarcted muscle must have taken place long before the last curves were made. Ordinarily, pronounced RS-T displacement of the kind in question persists for a few

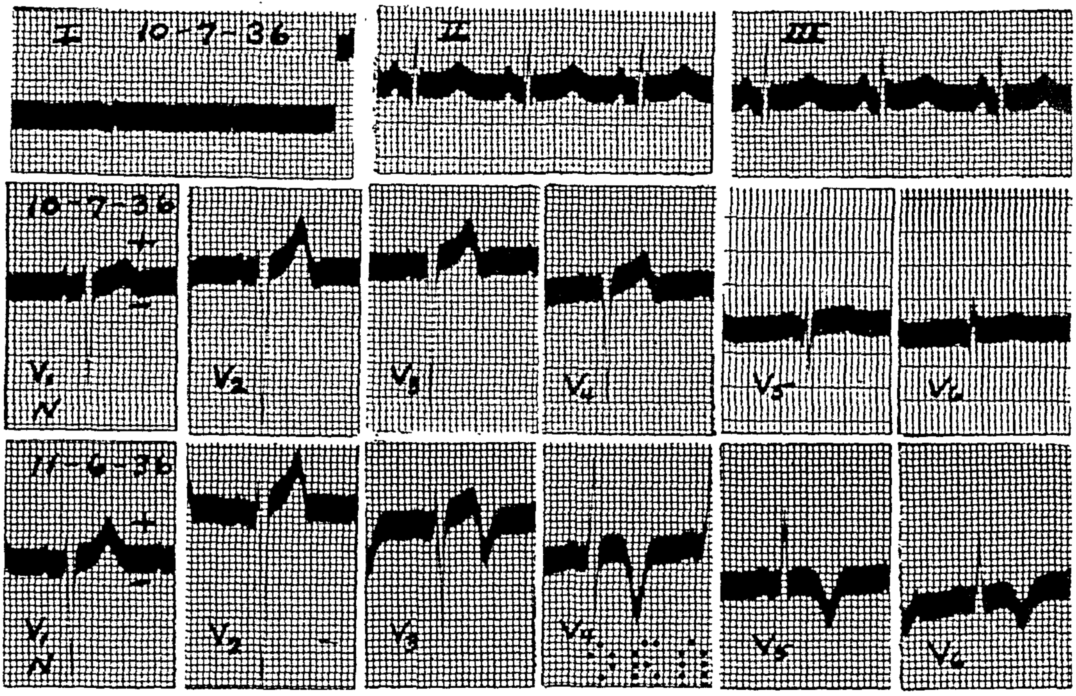
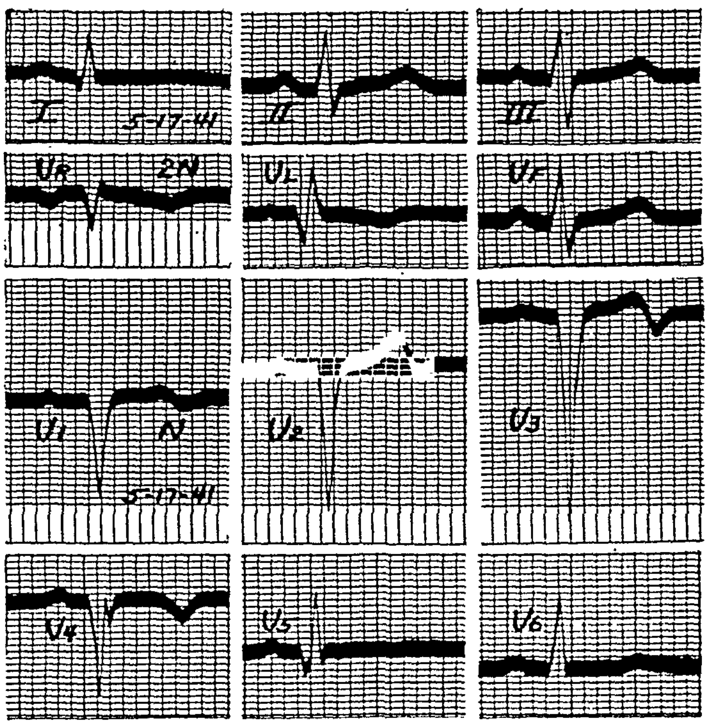


Fig. 23.—Anterior myocardial infarction; transient QRS changes.



Coronary occlusion 7 years ago.

Fig. 24.—Anterior myocardial infarction; persistent changes in the QRS complex and residual changes in the T waves.

hours, or, at most, for a few days. Why it persists in rare instances for weeks or months is still a mystery. In three cases of this sort, one of which was observed by Langendorf,[20] a ventricular aneurysm was present, but it is possible that the association was due to chance. There

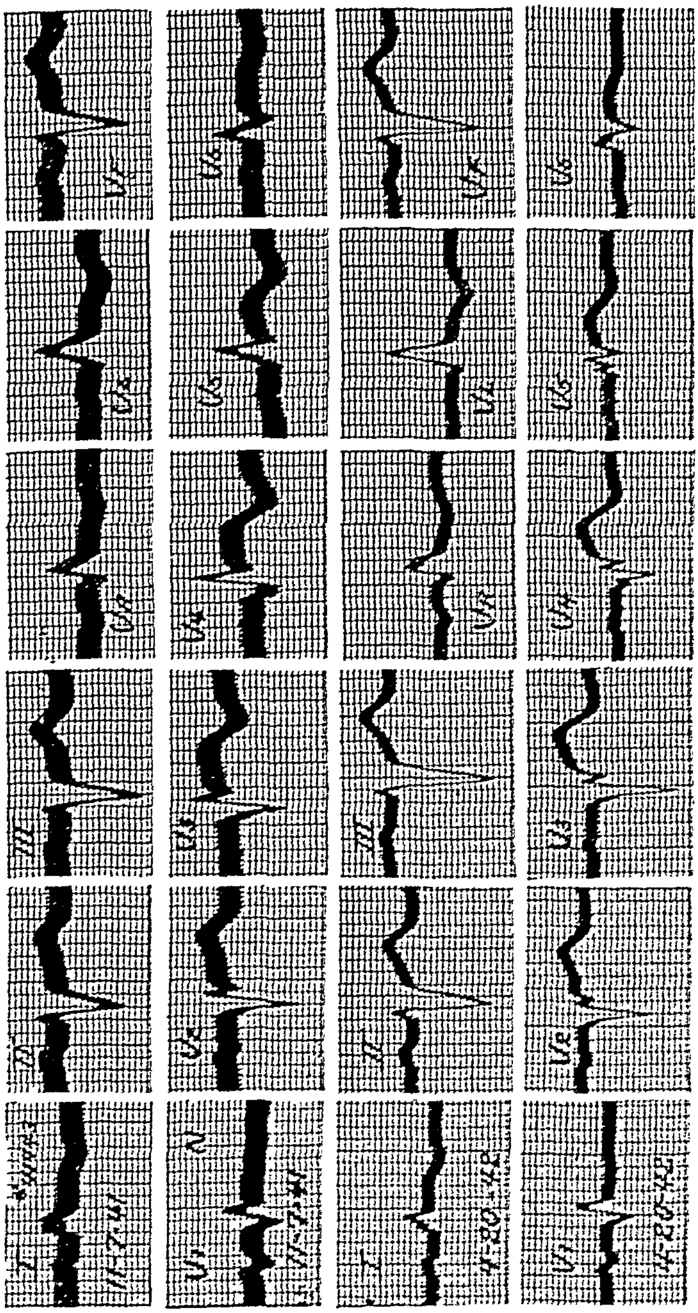


Fig. 25.—Anterior myocardial infarction: persistent RS-T displacement, incomplete right bundle branch block.

is no known reason why ventricular aneurysm should displace the RS-T junction or deform the RS-T segment in this way. In addition to RS-T displacement, both electrocardiograms display a QRS interval between 0.10 and 0.11 second in length, and late R waves in the leads from the right side of the precordium. These findings strongly suggest that incomplete right branch block was present.

Extensive Anterior Infarction.—In the three cases illustrated in Fig. 26, characteristic signs of infarction were present in all of the six precordial leads, or in all except the first. In such instances it must be assumed that the region involved is a very large one. The first patient was a woman, aged 48 years, who began to have symptoms typical of coronary thrombosis at 9:45 P.M. on Aug. 9, 1938. On the

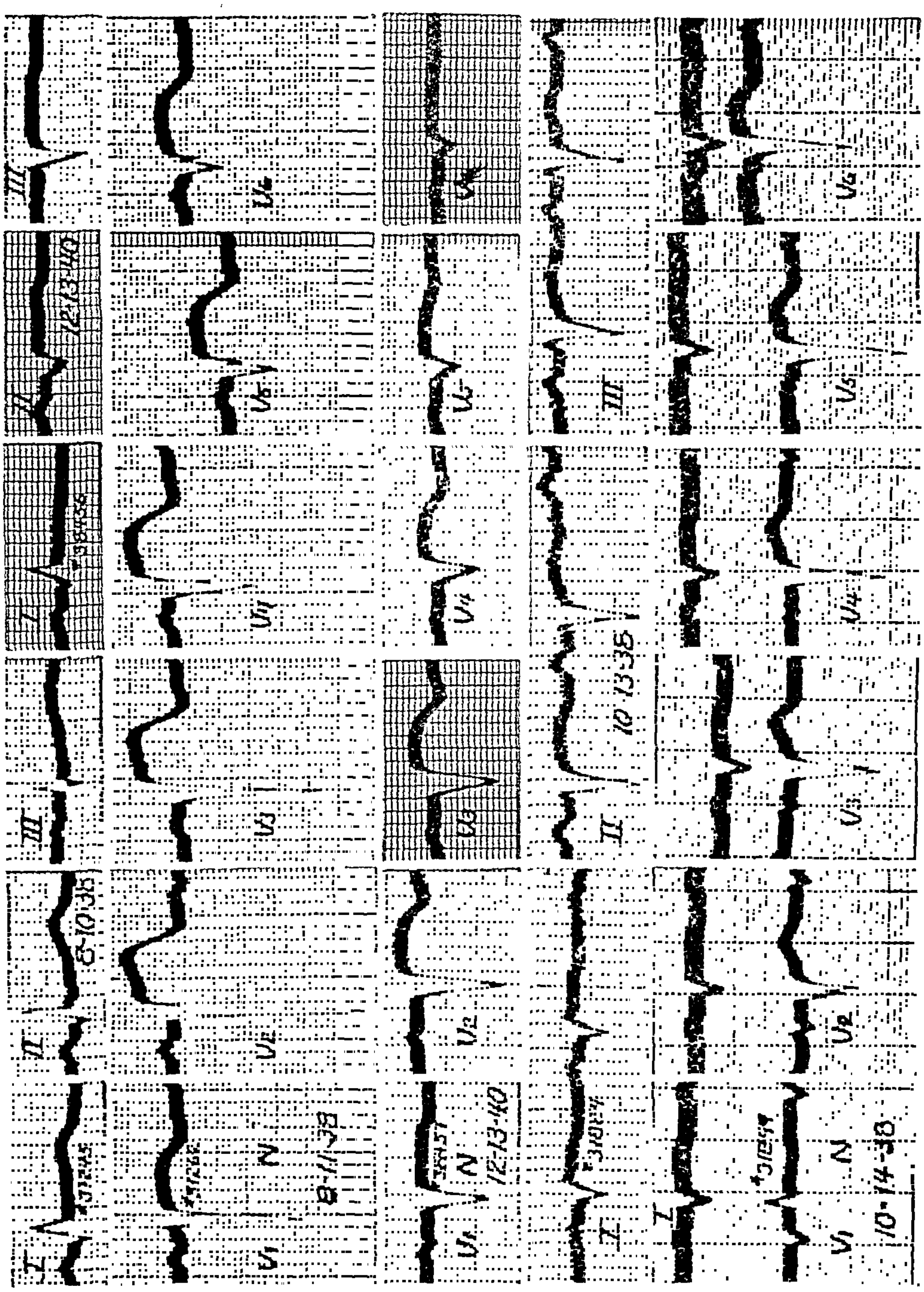


Fig. 26.—Three cases of extensive myocardial infarction.

next day, small QRS deflections, prominent Q waves, and upward displacement of the RS-T junction were present in Lead I. On August 11, the precordial electrocardiogram displayed large QS deflections and conspicuous upward RS-T displacement in all leads except V_1. The second patient was a man, aged 71 years, who began to have severe

pain in the chest at 9:45 P.M., on Dec. 10, 1940. On December 13, the changes in the precordial leads were almost identical with those that occurred in the case just described. Both patients recovered.

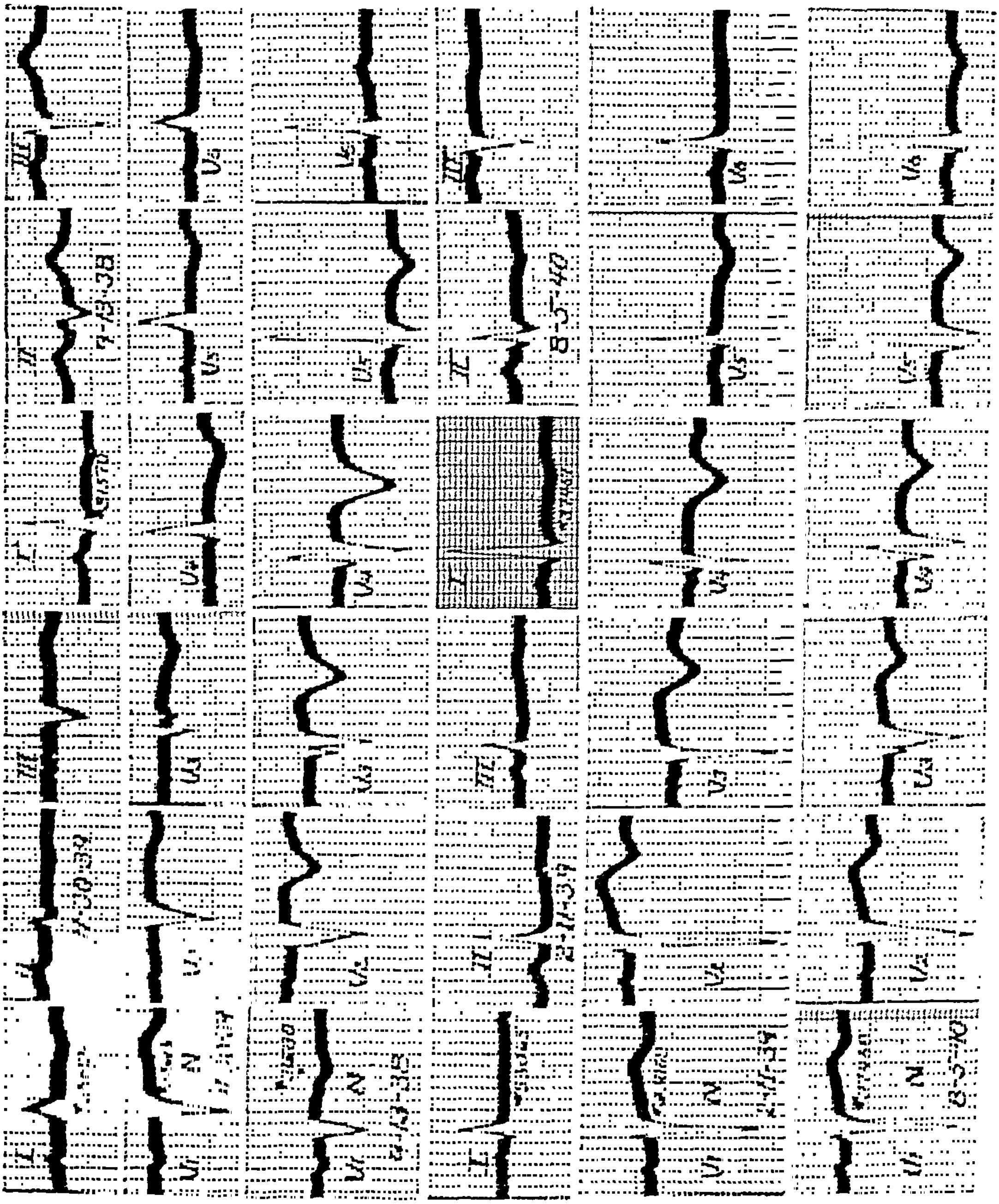


Fig. 27.—Four cases of anteroseptal infarction.

The third patient was a man, aged 48 years, who had severe attacks of anginal pain on Feb. 1, and on May 30, 1938. The first electrocardiogram was taken on Oct. 14, 1938. At that time there were very large Q deflections in Lead I and large QS deflections in the last five precordial leads. Probably because the infarct was an old one, no pronounced RS-T displacement or typical T-wave changes were present. The patient died on Oct. 16, 1938, and autopsy disclosed an infarct

measuring 9 by 10 cm., which involved the lower two-thirds of the anterolateral, and the lower one-third of the posterior, wall of the left ventricle. The cavity of this chamber was almost completely filled by a thrombus.

Anteroseptal Infarction.—In the four cases illustrated in Fig. 27, the diagnostic signs of infarction (characteristic QRS combined with characteristic RS-T or T-wave abnormalities) were confined to the leads from the right side of the precordium. Leads V_5 and V_6 display alterations in the T waves which are more or less typical but no unequivocal changes in the QRS complexes. Since the potential variations of the left arm are like those of the left side of the precordium in the majority of the cases of anterior myocardial infarction, the changes in the ventricular complexes of Lead I are as a rule no greater than those displayed by the ventricular complexes of Lead V_5. An electrocardiographic diagnosis of anterior infarction, therefore, cannot be made with certainty in cases of the kind under consideration unless leads from the right side of the precordium are employed. Since the potential variations of the infarcted region are referred to the right side of the precordium, we may assume that the anteroseptal wall of the left ventricle is involved.

The first patient was a man, aged 68 years, who developed myocardial infarction in September, 1939. The electrocardiogram, taken on November 30 of that year, shows notched QS deflections in Leads V_2 and V_3 and inversion of the T waves, not of the kind characteristic of infarction, in Leads I, V_3, V_4, V_5, and V_6. The ventricular complexes of Lead I closely resemble those of Lead V_6.

The second patient was a man, aged 57 years, who had a coronary accident about Sept. 1, 1938. The electrocardiograms, made on September 13, show characteristic changes in the T waves of Leads I, V_2, V_3, V_4, and V_5. Characteristic changes in the QRS complexes are confined to Leads V_2 and V_3. The ventricular complexes of Lead I are like those of Lead V_5.

The third patient was a woman, aged 48 years, who began to have symptoms typical of coronary thrombosis on Feb. 9, 1939. The electrocardiograms, taken on February 11, show signs diagnostic of infarction in Lead V_3 and typical T-wave changes in Lead V_4. The ventricular complexes of Lead I are like those of Lead V_6.

The fourth patient was a man, aged 59 years, who had a coronary occlusion on May 14, 1940. The electrocardiograms of Aug. 5, 1940, display signs diagnostic of infarction in Leads V_3 and V_4 and characteristic T-wave changes in Leads V_5 and V_6. The ventricular complexes of Lead I are like those of Lead V_6.

In normal subjects the R deflection steadily increases in height as the precordial electrode is moved from the first to the fourth position and

then decreases as it is moved farther to the left. The decrease in the height of R, and its eventual disappearance as the exploring electrode was moved across the right side of the precordium in a number of the cases just described, is a far more reliable sign of infarction than complete absence of this deflection in the first two or three precordial leads.

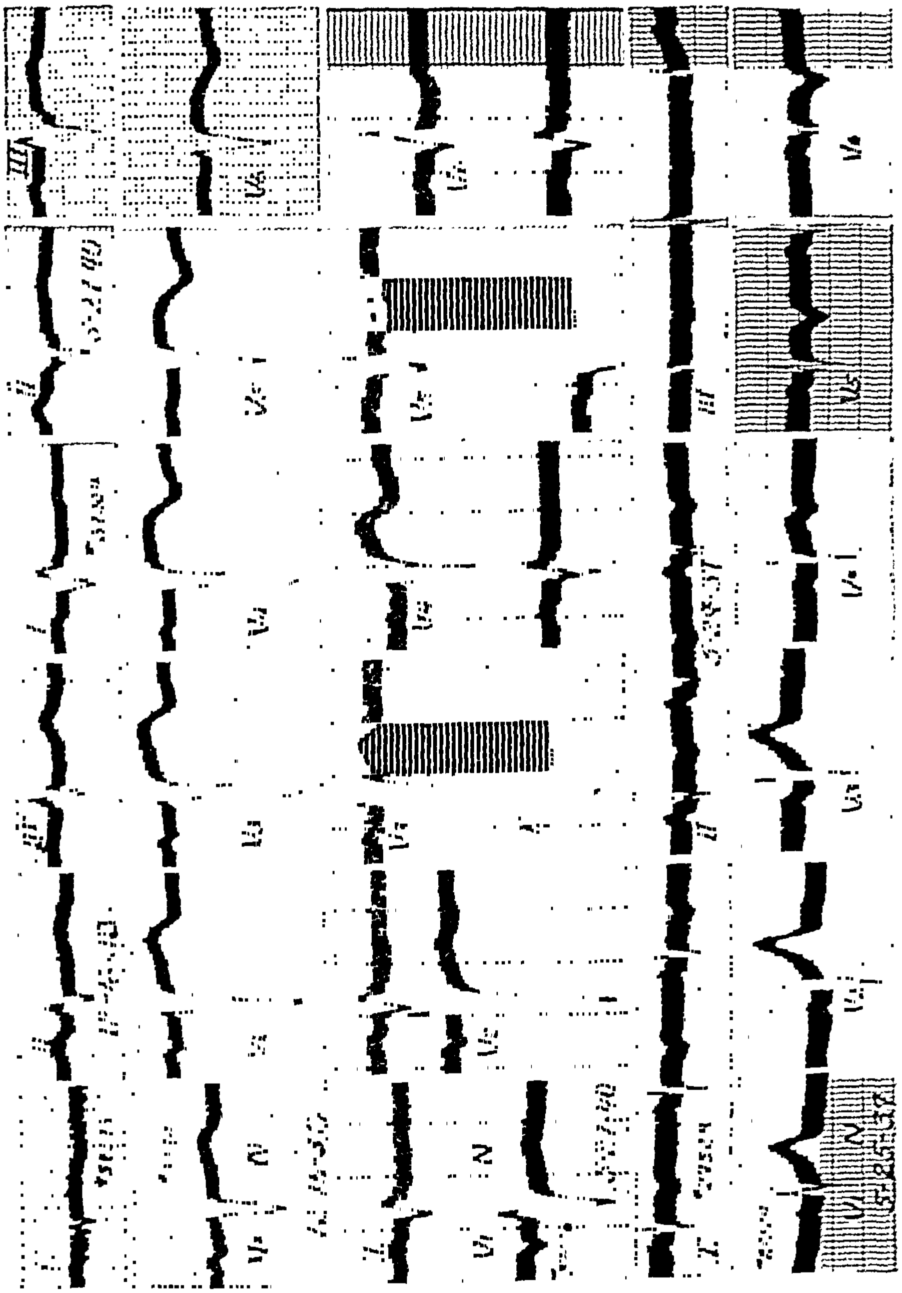


Fig. 28.—Two cases of anterolateral and one case of posterolateral infarction.

Anterolateral Infarction.—In the first two of the three cases illustrated in Fig. 28, the diagnostic signs of infarction in the chest leads are confined to the leads from the left side of the precordium, and it may be assumed that the anterolateral wall of the left ventricle was involved.

The first patient was a man, aged 70 years, who had a severe attack of anginal pain on July 6, 1938. The precordial electrocardiogram, taken on December 16 of the same year, displays signs diagnostic of infarction in Leads V_4 and V_5, and abnormally small R deflections associated with changes in the T complex in Lead V_6. In Lead I the QRS deflections are extremely small, and suggestive changes in the T waves are present.

The second patient was a man, aged 47 years, who was disoriented when admitted to the hospital, so that no history of his illness could be obtained. It was learned later that he had had anginal pain, but the time at which coronary thrombosis occurred could not be determined. The electrocardiogram displays deep Q deflections in Lead I and in Lead V_5, and the ventricular complexes of these leads are very much alike. There is also a rapid decrease in the size of the R deflection between Lead V_2 and Lead V_5. No characteristic modifications of the RS-T segment or T wave are present, probably because the infarct was an old one.

In infarcts of this kind, as a rule, there are changes diagnostic of infarction in the ventricular complexes of Lead I. Since the infarct involves the left upper margin of the heart, the potential variations at its epicardial surface are transmitted to the left arm.

The third case illustrated in Fig. 28 belongs to a different group and will be referred to later.

High Lateral Infarction.—The electrocardiograms reproduced in Fig. 29 are those of a man who was under observation off and on from September, 1926, until his death on Jan. 19, 1942. In the autumn of 1934, he began to have mild anginal pain on exertion after meals, and at 3 o'clock on the morning of Aug. 18, 1935, he developed symptoms characteristic of coronary thrombosis. The electrocardiogram taken on the following day presents small QRS deflections, deep Q waves, and sharply inverted T waves in Lead I. The precordial electrocardiogram taken at the same time, which is not reproduced, is not definitely outside normal limits, but the R and T waves of Leads V_1 and V_2 are unusually prominent. The patient had no more anginal pain and got along very well until June 3, 1940, at 12:30 P.M., when a second coronary accident occurred. The electrocardiogram taken two days later is very similar to that of 1935 except that the QRS interval is a little longer. Precordial leads were not used on this occasion. In October, 1941, paroxysmal nocturnal dyspnea began to occur, and in January, 1942, the patient entered the hospital with the symptoms and signs of congestive cardiac failure, and attacks of substernal oppression.

On January 13, the limb leads showed a QRS interval measuring approximately 0.11 second, left axis deviation, and inverted T deflections in Lead I. The precordial curves of the next day present a very small R deflection in Lead V_2 and prominent Q waves in Lead V_3, but no other changes which suggest infarction. The third attack of severe

anginal pain began at 7 A.M., on January 15. On January 17, right bundle branch block was present. The precordial leads then showed changes characteristic of this conduction defect and small bizarre QRS deflections in Lead V_2.

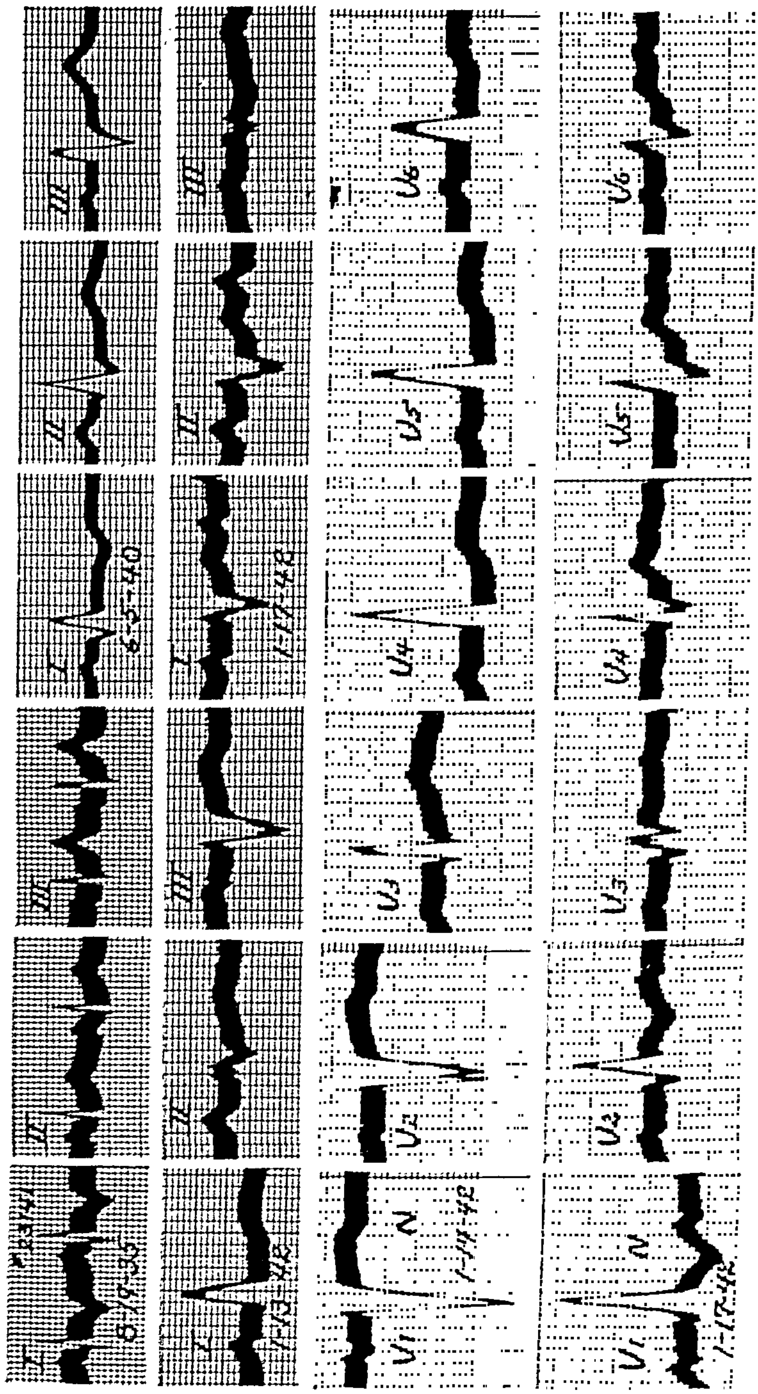


Fig. 29.—High lateral infarction (see text).

The autopsy disclosed a very large thrombus covering the apical two-thirds of the inner aspect of the anterior wall of the left ventricle. Beneath this clot the endocardium was grayish-white in color, and near the base of the ventricle it was about one millimeter thick. Mottled grayish-

pink to bluish-red areas were scattered through the anterior wall of the left ventricle, the septum, and the apical parts of the right ventricle, which also contained a thrombus. The left coronary artery was blocked by a fresh clot near its origin. In the posterolateral wall of the left ventricle near its base there were extensive grayish-white to grayish-yellow areas which were thought to represent old myocardial infarction. The infarct responsible for the electrocardiographic changes observed in 1935 and 1940 apparently involved this region. We have seen only one other instance in which the limb leads showed signs diagnostic of anterior infarction and the precordial leads did not.

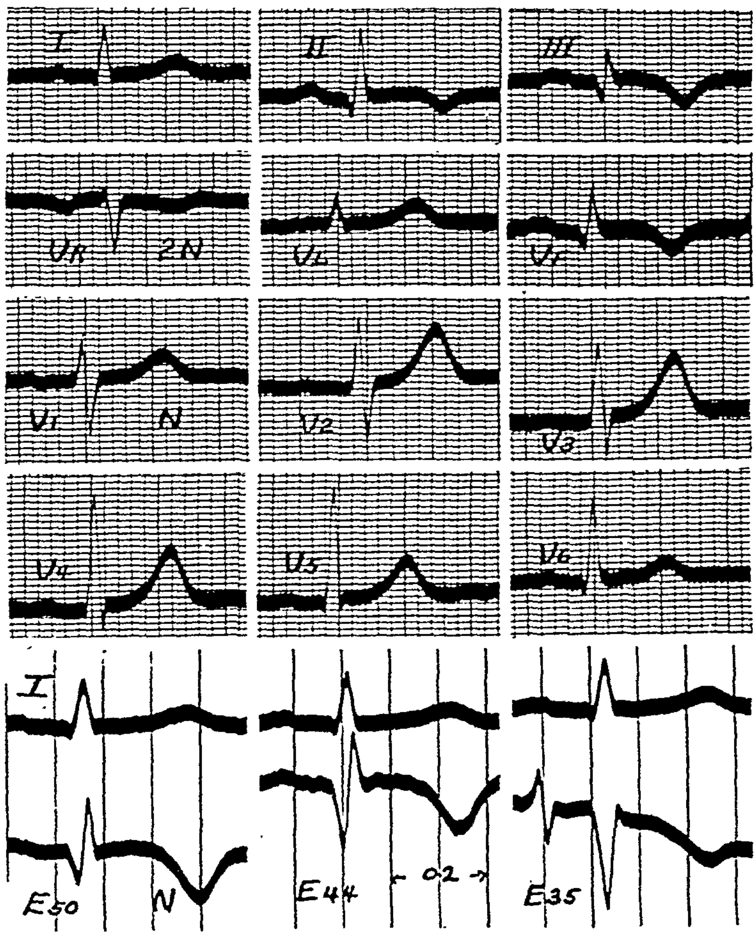


Fig. 30.—Plain posterior infarction. In this as in other figures the symbol *E* is used for unipolar esophageal leads. The figure which follows this symbol gives the distance (in centimeters) of the esophageal electrode from the nostrils.

Plain Posterior Infarction.—The man, aged 45 years, whose electrocardiograms are shown in Fig. 30, was referred to us for laboratory studies only. He had symptoms typical of coronary thrombosis about one month before these curves were taken. The deep Q waves and sharply inverted T waves of Leads II and III indicate that there was a recent infarct on the posterior wall of the heart. Note that the potential variations of the outer surface of the infarct were transmitted to the left leg. The precordial leads show no significant abnormalities, but it will be observed that, in Leads V_1 and V_2, the R deflections and T waves are unusually tall. Characteristic signs of infarction are present

in the leads from the ventricular levels of the esophagus (Leads E_{44} and E_{50}). In the lead from the auricular levels of the esophagus (Lead E_{35}), there is a large diphasic auricular complex, and the ventricular complex consists of a large QS deflection followed by an inverted T wave. Electrocardiograms of this kind are obtained from the auricular levels of the esophagus in normal subjects.[21] The exploring electrode is close to the auricular wall, which accounts for the character of the auricular complex, and also opposite the great valvular orifices at the base of the ventricles so that the negativity of the ventricular cavities is transmitted to it. Large Q or QS deflections in leads from this region have no significance.

In the earliest stages of infarction of the posterior wall of the heart, downward displacement of the RS-T junction is usually present in the precordial leads. In leads from the ventricular levels of the esophagus, the displacement is upward.[21]

Posterolateral Infarction.—The last of the three patients whose electrocardiograms are reproduced in Fig. 28 was a physician, aged 42 years, who had a coronary accident on March 18, 1937. The limb leads, taken on May 25 of the same year, display inverted T waves in Leads I and II and small QRS deflections with prominent Q waves in Leads II and III. There is also a small Q deflection in Lead I. The changes in the T waves resemble those found in anterior, and the changes in the QRS complex those found in posterior, infarction. In the precordial curves, the significant abnormalities are in Leads V_5 and V_6, which show prominent Q and sharply inverted T waves. It will be noted, however, that in the leads from the right side of the precordium, the R and T deflections are unusually prominent.

Another electrocardiogram of the same sort is reproduced in Fig. 31. The patient was a man, aged 54 years, who had symptoms typical of coronary thrombosis about one month before the electrocardiographic study was made. In this instance, unipolar leads from the left posterior axillary line, from the left infrascapular region, and from the ventricular levels of the esophagus were taken, and all of these show prominent Q and sharply inverted T waves. Similar but less characteristic changes are present in the leads from the left side of the precordium (Leads V_5 and V_6). There can be little doubt that the infarct involved the posterolateral wall of the heart. Note that here also large Q and inverted T waves occur in the unipolar left leg lead. Not all cases in which there are sharply inverted T waves in Lead I and abnormally large Q waves in Leads II and III are examples of posterolateral infarction. This electrocardiographic pattern in the limb leads may be produced by the simultaneous presence of two infarcts, an old lesion on the posterior, and a more recent one on the anterior, wall of the heart. It may also occur in anteroseptal infarction in which, perhaps because of some peculiarity in the position of the heart or because there is more

involvement of the septal wall of the left ventricle than is usual, the potential variations of the central part of the infarcted ventricular wall are sometimes transmitted to the left leg.

Posteroinferior Infarction.—The electrocardiograms reproduced in Fig. 32 are those of a man, aged 53 years, who had symptoms typical of coronary occlusion on Dec. 19, and Dec. 23, 1941. The curves taken

Fig. 31.—Posterolateral infarction.

on December 26 show upward displacement of the RS-T junction, sharply inverted T waves and prominent Q deflections in Leads II, III, and V_F, and complete atrioventricular block, which was transient. Signs diagnostic of infarction are present in the unipolar lead from the tip of the ensiform cartilage (Lead V_E), but in none of the usual precordial leads. It will be noted that, in this instance, the R and T waves are not unusually prominent in the leads from the right side of the precordium. On the contrary, no R wave is present in Lead V_1, and the R wave in Lead

V_2 is unusually small. In some cases of this sort, slight upward displacement of the RS-T junction occurs in Lead V_1 in the early stages of infarction.

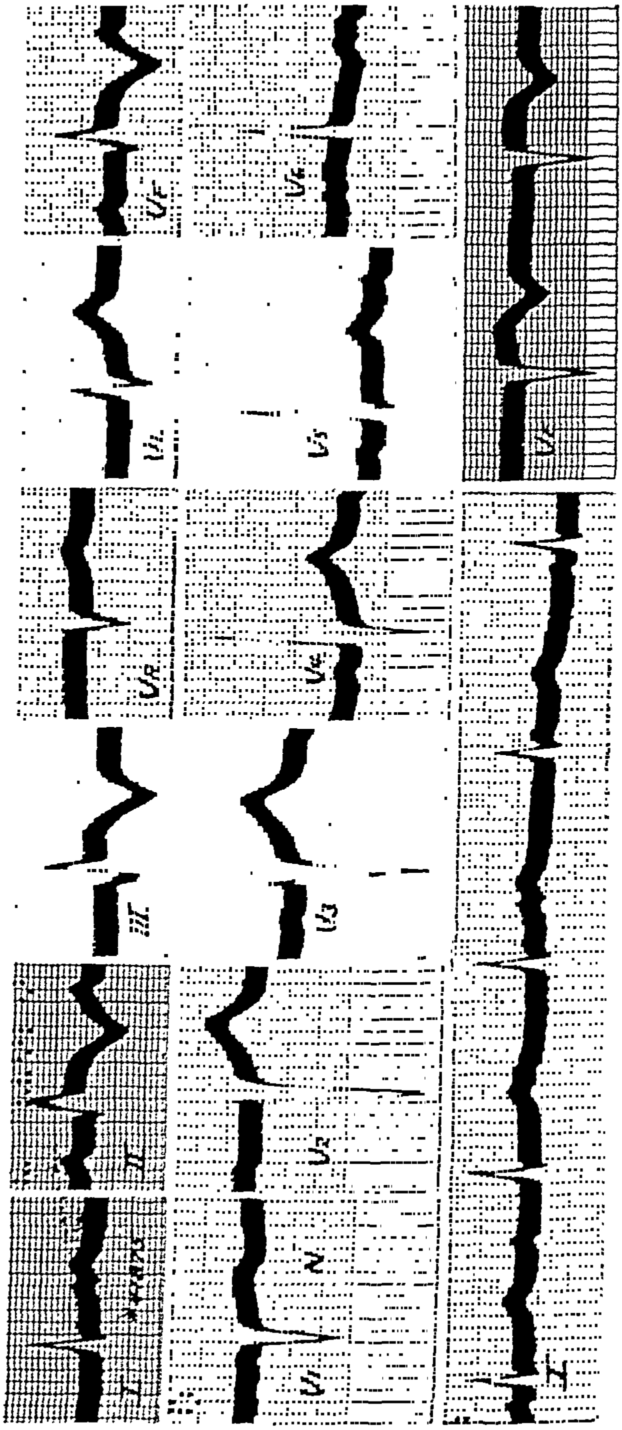


Fig. 32.—Posteroinferior infarction.

Signs of Posterior Infarction in Limb Leads and of Anterior Infarction in the Precordial Leads.—We have seen only one case of the kind illustrated in Fig. 33. The patient, a man aged 68 years, had a coronary accident on March 31, 1935, while he was under treatment for prostatic hypertrophy. He died three days later, but permission for an autopsy

could not be obtained. No symptoms referable to the heart had occurred previous to this fatal illness. The limb leads show pronounced upward displacement of the RS-T junction and prominent Q deflections in Leads II and III and in precordial Lead V_3. There is, in addition, conspicuous RS-T displacement without characteristic alterations of the QRS complex in Leads V_2 and V_5. Leads V_4 and V_6 were not taken.

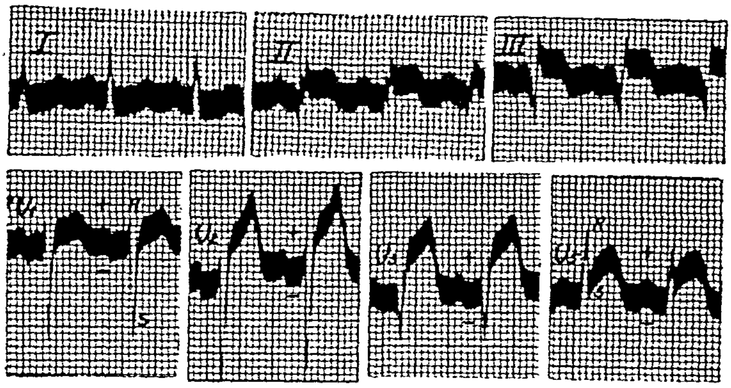


Fig. 33.—Signs of posterior infarction in the limb leads and of anterior infarction in the precordial leads. (After Wilson.[22] Reproduced with the permission of the Macmillan Company, New York.)

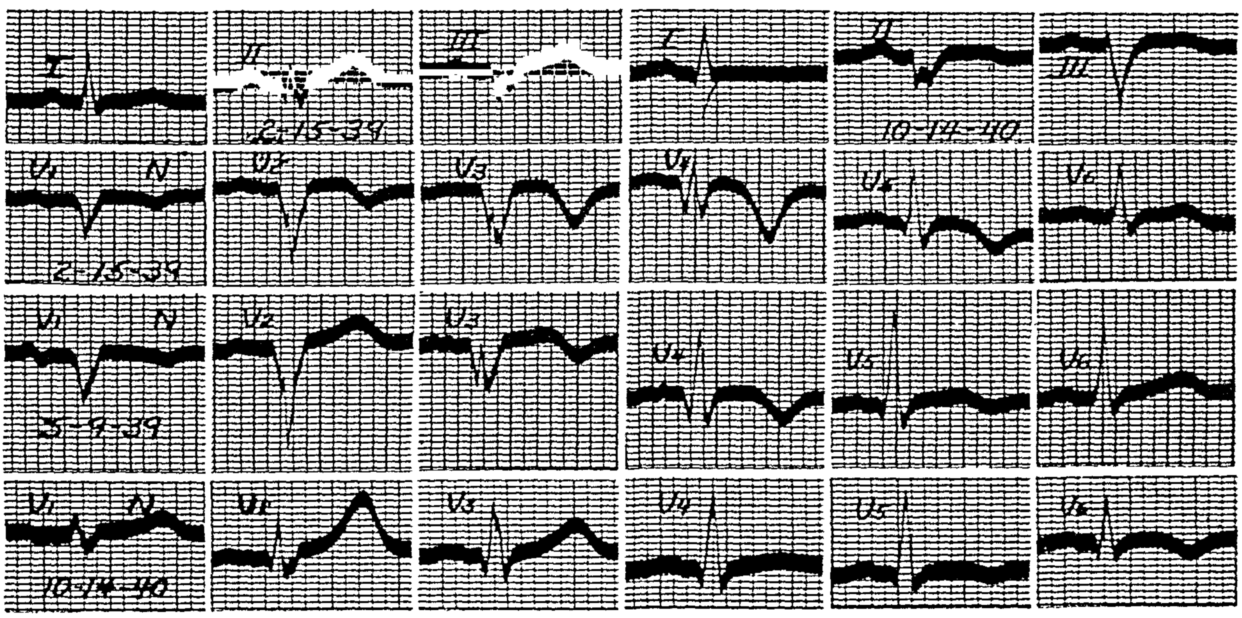


Fig. 34.—Anteroseptal followed by posterolateral infarction.

The character of the electrocardiographic changes precludes the possibility that there were two infarcts differing in age. Nor does it appear consistent with the presence of a single infarct extending from the posterior wall of the heart around the left margin onto the anterior wall, for the most striking changes in the precordial leads are in the middle of the series. We are not able to explain these findings satisfactorily, but may point out that apical infarction might give rise to electrocardiographic changes of this sort if the heart were in the vertical position.

Old Anteroseptal and Recent Posterolateral Infarction.—The electrocardiograms reproduced in Fig. 34 are those of a man, aged 52 years, who had symptoms characteristic of infarction on Dec. 18, 1938, and

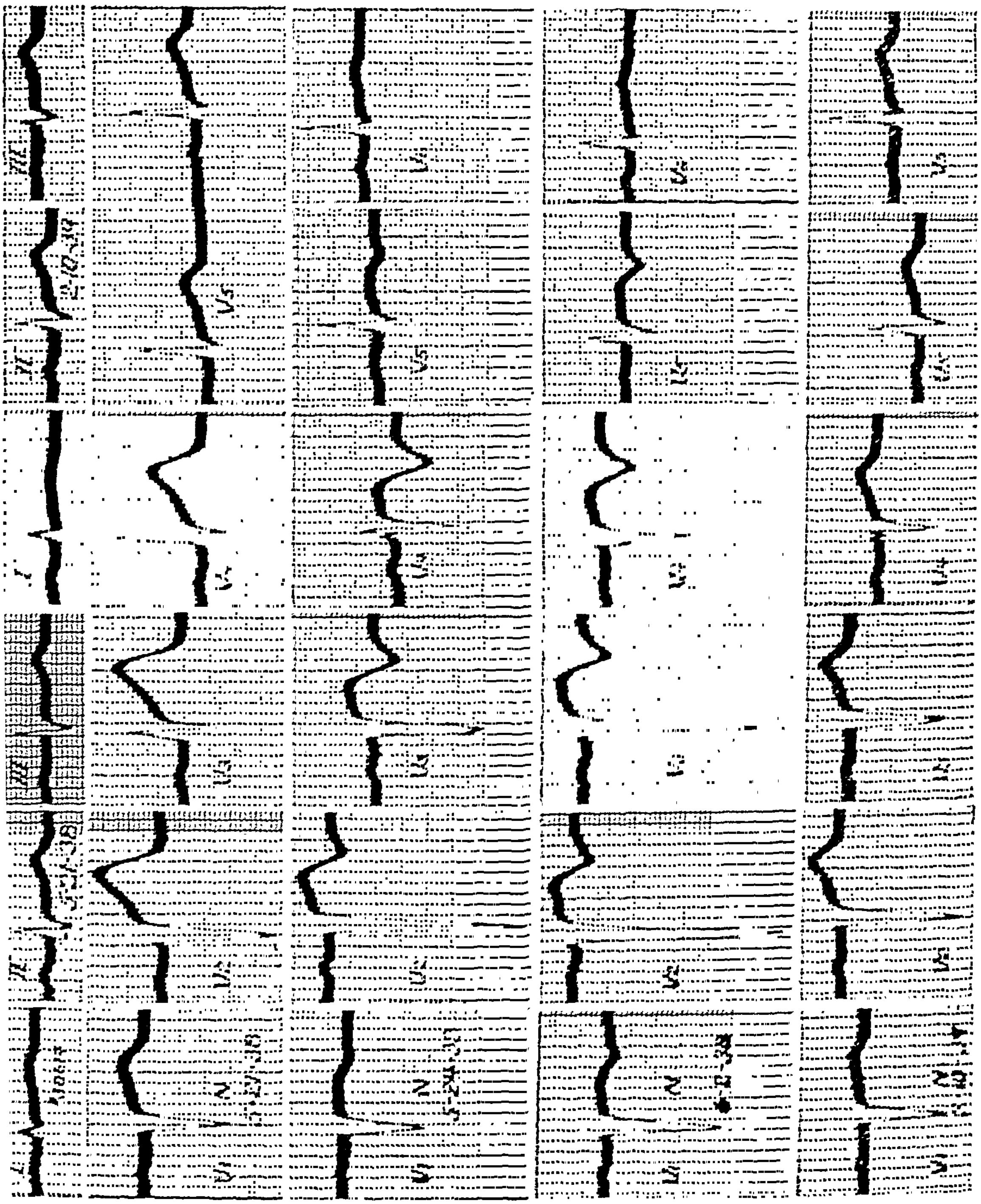


FIG. 35.—Serial electrocardiograms in a case of anteroseptal infarction.

made an uneventful recovery. On Aug. 29, 1940, he had a second attack of severe anginal pain. On this occasion he was examined at his home and the cardioscope disclosed very pronounced upward RS-T displacement in Leads II and III.

The electrocardiograms taken two months after the first attack show prominent Q deflections but no characteristic T-wave changes in Leads II and III. The precordial curves of the same date display signs diagnostic of infarction in Leads V_2, V_3, and V_4, and sharply inverted T waves in Lead V_5. Note that the ventricular complexes of Lead I resemble those of Lead V_6 which are in no way abnormal. The infarct was, then, of the anteroseptal variety. We have already mentioned that infarcts of this kind may give rise to prominent Q deflections in Leads II and III. After the second infarction, sharply inverted T waves appeared in the complexes of Lead V_6 which had previously escaped modification, and initial R deflections were present in Leads II and III. At the same time, conspicuous R waves were found in the leads from the right side of the precordium in which only embryonic R deflections had previously been present. Note, however, that the resurgent R waves are preceded by Q deflections in Leads V_2, V_3, and V_4. Observe also the large size of the T waves in Leads V_1, V_2, and V_3, in which deeply inverted T waves were present after the first coronary accident. The second infarct was, then, of the posterolateral kind.

We were able to make a more detailed study of another case in which the same series of events occurred. The patient was a man, aged 48 years, who had his first coronary thrombosis on May 21, 1938. The first electrocardiogram was taken about two hours after the onset of characteristic symptoms (Fig. 35). The limb leads showed no significant changes, but there was very pronounced upward displacement of the RS-T junction in Leads V_2, V_3, and V_4. Three days later, the R deflections had disappeared in Leads V_1, V_2, and V_3 and had become very small in Lead V_4, the RS-T displacement had begun to subside, and inversion of the terminal part of the T waves had developed in Leads V_1, V_2, V_3, V_4, and V_5. The ventricular complexes of Lead V_6 were not affected. In the course of the next year the T deflections regained their normal form, but the QRS changes persisted.

On March 5, 1942, the patient, who had been well for nearly three years, began to have new attacks of severe anginal pain. He was admitted to the hospital, but at first the electrocardiogram showed only the residual changes which dated from his first infarction (Fig. 36). On March 11, however, he developed clear signs of posterior infarction. In the extremity curves, these consisted of pronounced upward displacement of the RS-T junction and prominent Q deflections in Leads II and III. In the precordial electrocardiogram, inverted T waves eventually developed in the complexes of Lead V_6, which had escaped in the first attack, and small R waves appeared in Leads V_1, V_2, and V_3. In these same leads the T waves became larger than they had been before.

Anterior Infarction Plus Right Bundle Branch Block.—When anterior infarction produces right bundle branch block, modifications of the electrocardiogram that can be regarded as diagnostic of infarction are relatively rare in the limb leads. Displacement of the RS-T junction and

more or less characteristic changes in the T waves may be present, but, when the area of the QRS complex is large, they are often obscured by the alterations in the T complex due to the block. In the precordial leads, on the other hand, entirely characteristic modifications of the QRS

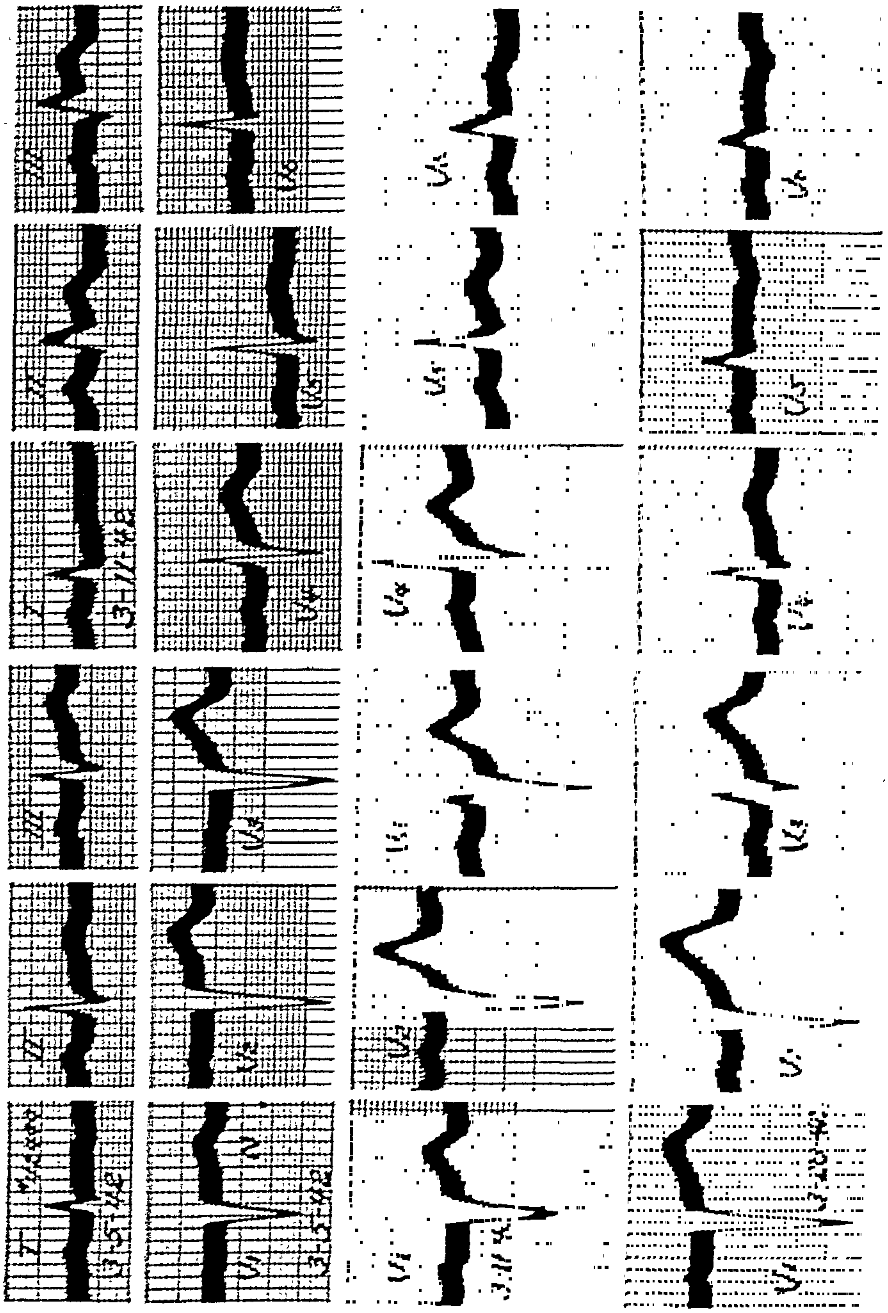


Fig. 39.—Serial electrocardiograms showing posterolateral infarction following anteroseptal infarction. (From the same case as Fig. 38.)

and T deflections are usually present. We have studied this problem experimentally by producing anterior infarction and right bundle branch block in dogs, and there are no essential differences between this animal and man, either as regards the character of the changes in the ventricular complexes of the limb leads, or as regards the changes of the ventricular deflections of precordial leads.

The electrocardiograms reproduced in Fig. 37 are those of a man, aged 37 years, who had severe attacks of anginal pain on July 26 and 28, 1938. Two days after the last attack, a pericardial friction rub was heard. The patient died on Sept. 18, 1938, and autopsy disclosed thrombosis of the anterior descending coronary artery and a very large anterior infarct over which the pericardium had become adherent. Liquefaction necrosis of the central part of the infarct had taken place.

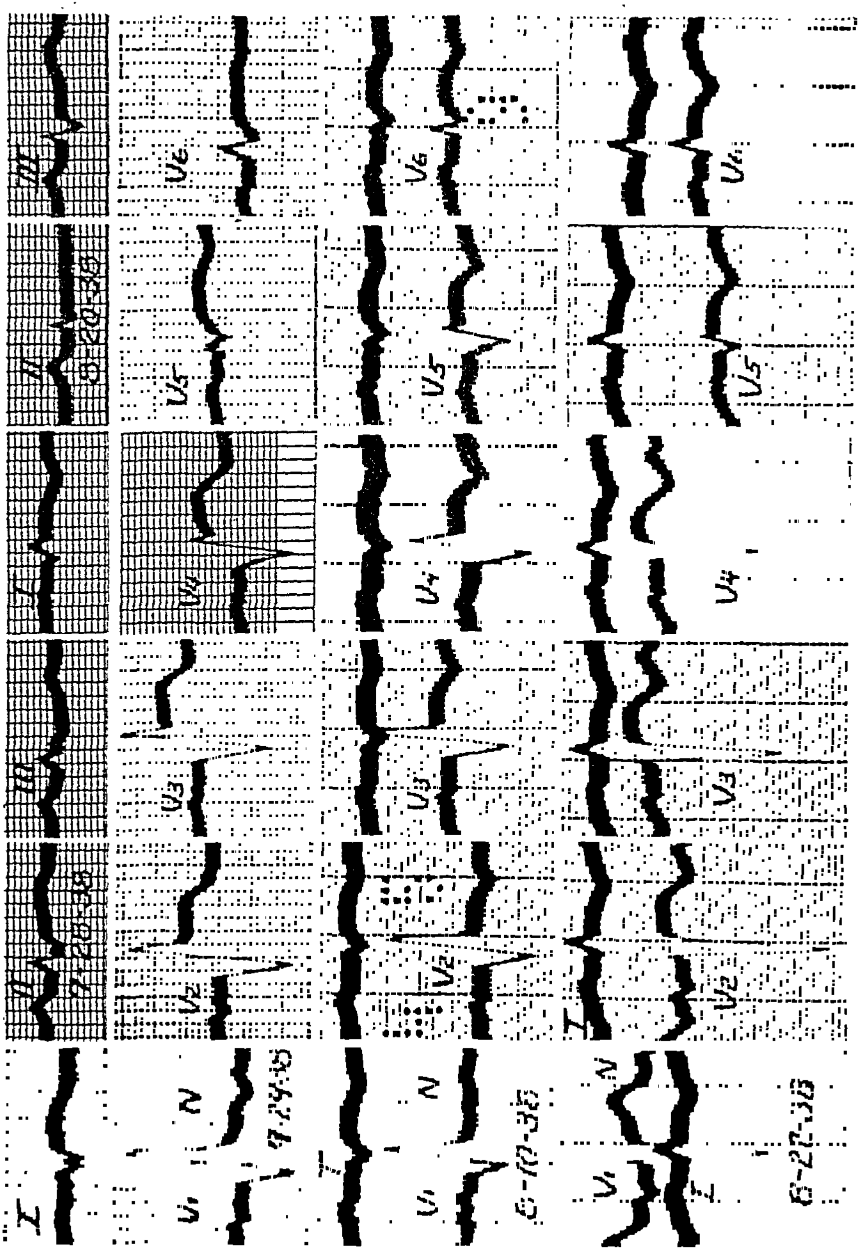


Fig. 37.—Anterior infarction complicated by transient right bundle branch block.

The limb leads, taken on July 28, show small broad QRS complexes and slight upward displacement of the RS-T junction in Lead I. The QRS interval measures approximately 0.12 second. The precordial curves taken on the following day are characteristic of anterior infarction complicated by right bundle branch block. The presence of the block is indicated by the length of the QRS interval, the very late R waves in Leads V_1, V_2, and V_3, and the broad S waves in Lead V_6. The small

initial R deflections which occur in the leads from the right side of the precordium in uncomplicated right bundle branch block are absent. The presence of the infarct is indicated by the very large Q deflections in Leads V_1, V_2, V_3, and V_4, the small bizarre QRS deflections in Lead V_5, and pronounced upward displacement of the RS-T junction in Leads V_2, V_3, and V_4. The precordial curves, taken on August 10, are not essentially different in general outline, but the RS-T displacement is not so great and the end of the T wave is slightly inverted in Leads V_2 to V_6 inclusive.

The electrocardiograms, taken on August 22, are very different. The QRS interval is normal, and small QRS deflections, prominent Q waves, and sharply inverted T waves are present in Lead I. In the precordial leads, the R deflection decreases from Lead V_1 to Lead V_4 where it is absent, and there are abnormally large Q deflections in Lead V_5. Displacement of the RS-T junction and inversion of the end of T are present in Leads V_2 to V_6. It is noteworthy that, although initial R waves were not present in Leads V_1, V_2, and V_3 so long as the branch block persisted, they appeared when normal intraventricular conduction was re-established. It should also be noted that the S waves which follow these small initial R deflections are much deeper than the Q waves present in the same leads during block. These initial R waves must evidently be ascribed to forces produced by activation of the free wall of the right ventricle, and the deep S waves that follow them, at least in part, to the activation of septal muscle from the right side.

Another example of anterior infarction plus right bundle branch block is illustrated in Fig. 38. The patient was a man, aged 56 years, who had a coronary thrombosis, either on Sept. 23 or on Oct. 3, 1938. The first electrocardiogram, taken before he had had anginal pain, is normal. After the coronary accident, the limb leads disclosed the presence of right branch block but showed no changes characteristic of myocardial infarction. The precordial curves, on the other hand, are characteristic of both of these conditions.

Posterior Infarction Plus Right Bundle Branch Block.—The electrocardiograms reproduced in Fig. 39 are those of a man, aged 53 years, who began to have symptoms characteristic of coronary thrombosis at 9 A.M. on April 30, 1941. The electrocardiograms, taken on May 27, 1941, display large Q waves in Leads II and III, and sharp inversion of the end of T in the latter. The QRS interval measures about 0.14 second and there is a broad S wave in Lead I. The precordial electrocardiogram is characteristic of right bundle branch block. The conspicuous Q waves and T-wave changes in Lead V_6 suggest that the marginal parts of the infarct involved the lateral wall of the left ventricle. In the cases we have observed, QRS changes in the limb leads characteristic of posterior infarction have not been obscured by the presence of right branch block.

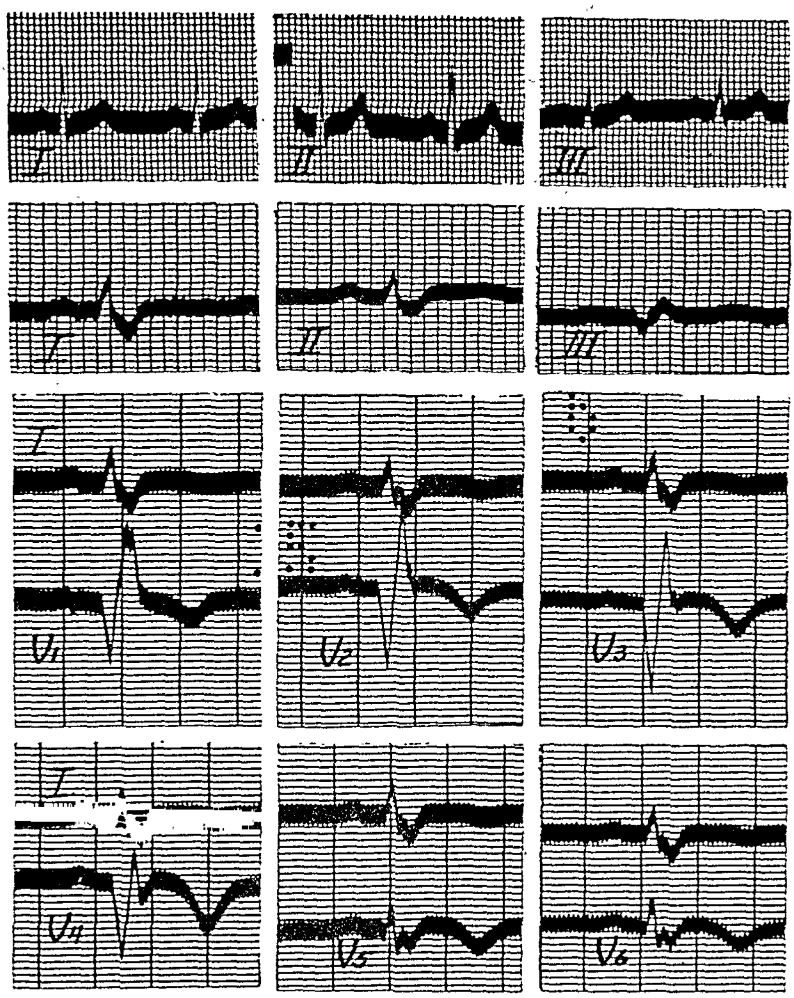


Fig. 38.—Anterior infarction complicated by right bundle branch block.

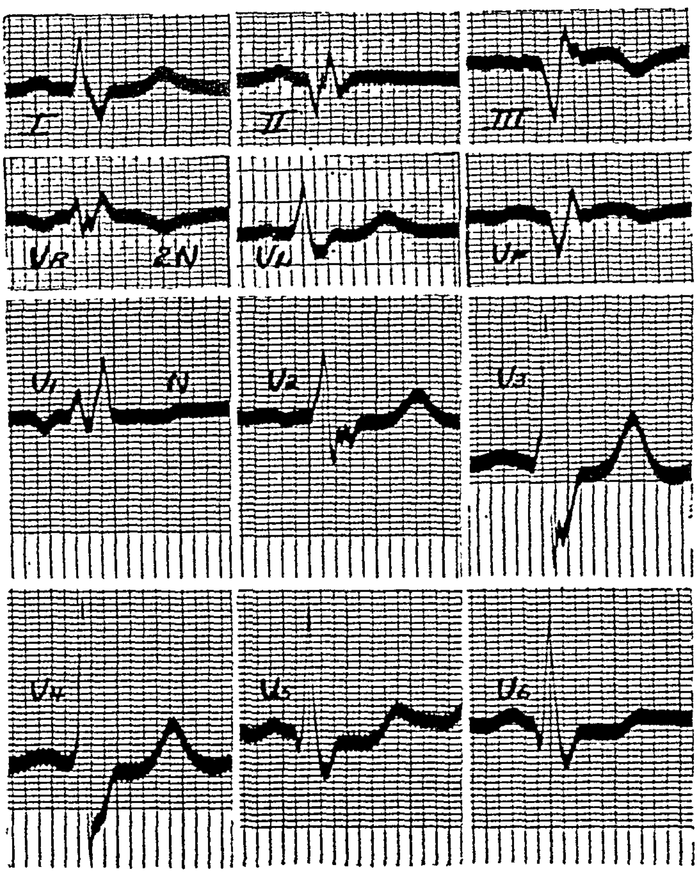


Fig. 39.—Posterior infarction complicated by right bundle branch block.

Myocardial Infarction Complicated by "Arborization" Block.—The electrocardiograms reproduced in Fig. 40 are those of a man who, after nine years of hypertension, developed myocardial infarction on Aug. 28, 1941. In the electrocardiograms of May 5, 1942, the limb leads display a QRS interval of about 0.14 second, deep, broad Q waves followed by

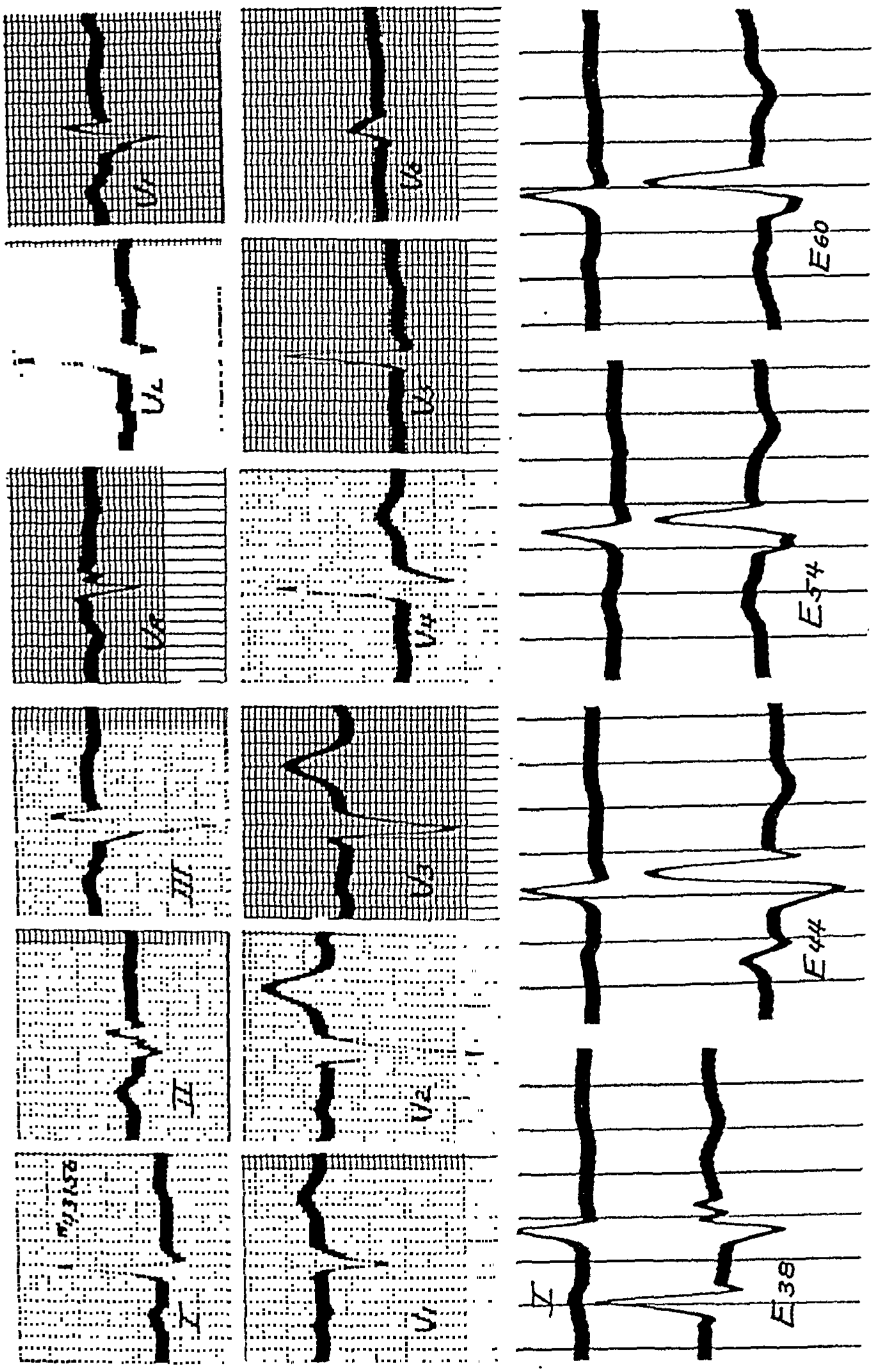


Fig. 40.—Posterior infarction complicated by "arborization" block.

late R waves in Leads II and III, and conspicuous S deflections in Lead I. This electrocardiographic pattern is very similar to that shown in Fig. 39, and posterior infarction complicated by right branch block was suspected. The precordial electrocardiogram, however, is incompatible

with the presence of this conduction defect, and shows no changes diagnostic of infarction; nor is it characteristic of left branch block. The leads from the ventricular levels of the esophagus (E_{44}, E_{54}, and E_{60}) present very broad, notched Q waves and very late, tall R deflections. It seems probable, therefore, that the infarct involved the subendocardial muscle on the posterior wall of the heart, and not only permitted the negativity of the left ventricular cavity to be transmitted to its epicardial surface during the first part of the QRS interval, but also delayed the activation of less seriously injured outer layers of muscle, which gave rise to the late R deflection.

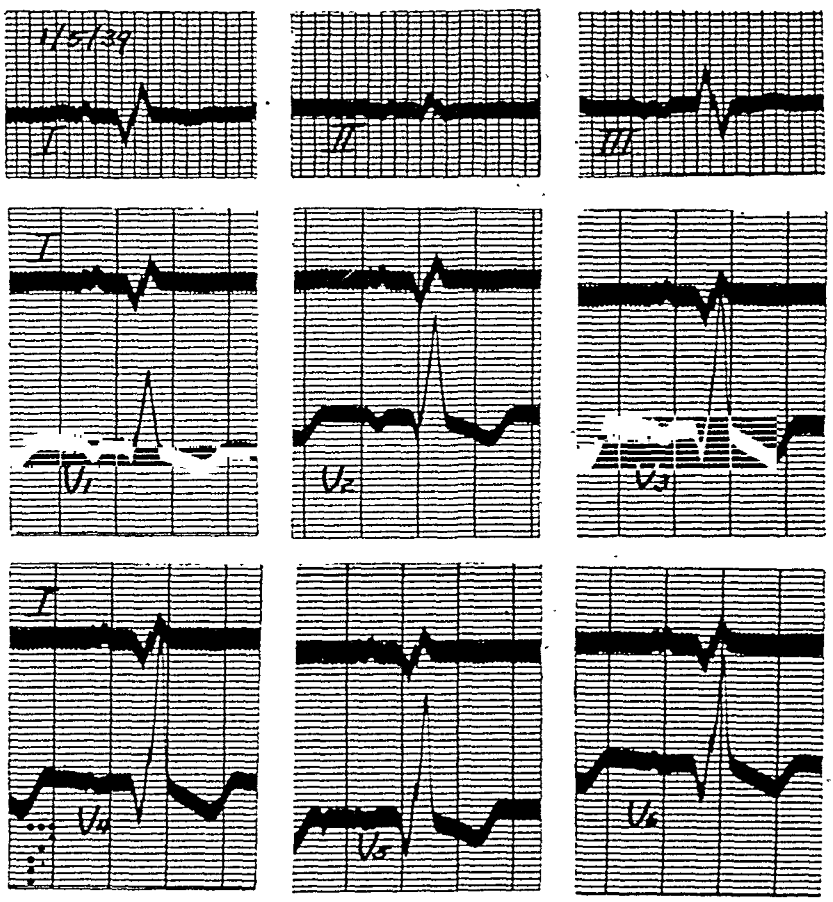


Fig. 41.—Anterior infarction complicated by "arborization block," by right bundle branch block, or by both.

The electrocardiograms reproduced in Fig. 41 are those of a man, aged 45 years, who had symptoms typical of coronary thrombosis, in January, 1938. The limb leads, taken a year later when the patient had congestive cardiac failure, display a QRS interval measuring between 0.11 and 0.12 second, small QRS deflections, and deep, broad Q waves in Lead I. The curves from the right side of the precordium are like those seen in right bundle branch block complicated by anterior infarction, but in this instance the curves from the left side of the precordium are of the same type. It will be noted that these ventricular complexes closely resemble the ventricular complexes of the esophageal electrocardiograms

reproduced in Fig. 40. In the case under consideration, leads from the ventricular levels of the esophagus yielded curves of the opposite type; the QRS complex of these tracings is diphasic and consists of an R wave followed by an S deflection of approximately equal size. It may be that these electrocardiograms represent right bundle branch block complicated by anterior infarction in which there is extreme displacement of the transitional zone. They are, however, more suggestive of anterior infarction with involvement of the subendocardial muscle over a large area, complicated by delayed activation of more normal subepicardial muscle and, perhaps, by right branch block as well. It seems probable that, in some cases of old infarction, the Purkinje network is damaged locally by subendocardial sclerosis and that, as a result, there is a delay in the activation of such living muscle as may remain in the part of the ventricular wall affected. Oppenheimer and Rothschild[16] had such lesions in mind when they introduced the term "arborization" block, but we doubt very much that the criteria for the electrocardiographic diagnosis of this condition advanced by them are capable of distinguishing between bundle branch block and intraventricular block of other types.

Infarction Complicated by Left Bundle Branch Block.—When coronary thrombosis is complicated by left bundle branch block, the electrocardiogram rarely presents changes which can be considered diagnostic of myocardial infarction. Displacement of the RS-T segment and changes in the T wave may occur if the area of the QRS complex is small. When the area of the QRS complex is large, the alterations in the T complex due to infarction are likely to be obscured by those produced by the conduction defect. The presence of characteristic modifications of the QRS deflections in infarction almost always depends upon the transmission of the potential variations of the cavity of the left ventricle to the epicardial surface of the infarct and the adjacent parts of the body. When this cavity is negative throughout the QRS interval, as is the case when intraventricular conduction is normal and in right bundle branch block, large Q or QS deflections occur in those leads in which one electrode is placed on that side of the left ventricle on which the infarct lies, provided that the connections are made in such a way that negativity of this electrode is represented by a downward deflection. In left bundle branch block, the cavity of the left ventricle is positive at the beginning of the QRS interval, and, consequently, Q or QS waves do not occur in leads of the kind mentioned. Direct or semidirect leads from the infarcted wall or from the cavity of this chamber display diphasic QRS complexes consisting of an R followed by an S deflection. Ventricular complexes of this sort are not sufficiently distinctive to have diagnostic value. When the septum is infarcted, as well as the free wall of the left ventricle, the cavity of the left ventricle is initially negative because the negativity of the cavity of the right is transmitted to it. Under these circumstances, the electrocardiogram may display large Q

or QS deflections in leads from the left precordium. The presence of large Q waves in these leads in left bundle branch block should always lead to the suspicion that the ventricular septum is involved.

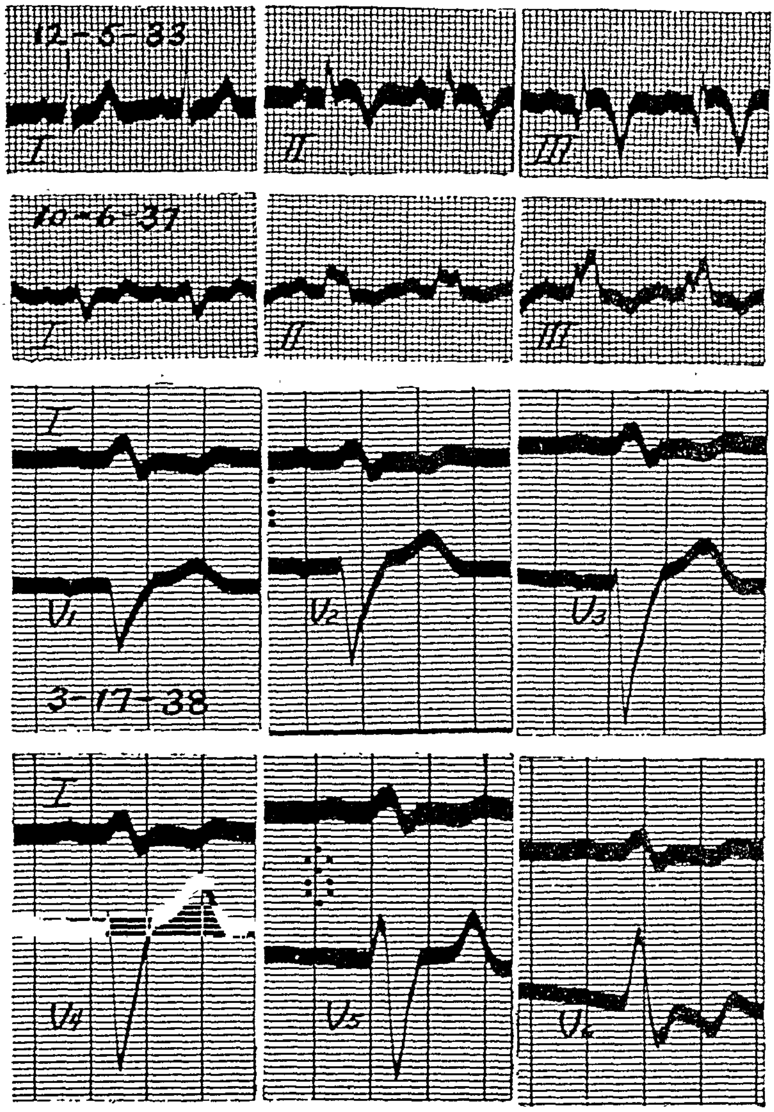


Fig. 42.—Posterior infarction complicated by left bundle branch block.

A case of infarction which was complicated by left bundle branch block is illustrated in Fig. 42. The patient was a man, aged 56 years, who had a coronary occlusion on Nov. 24, 1933. When he was first seen about ten days later, the limb leads showed the changes usually observed in posterior infarction. Except for inversion of the T waves in Lead V_6 the precordial leads were negative. A week later, the patient developed transient intraventricular block with ventricular complexes similar to those observed in 1937 and 1938 (see Fig. 42). The area of the QRS group was small, and the block did not abolish the inverted T waves in Leads II and III. It did abolish the prominent Q waves in these leads. These curves have been published (Wilson,[22] Fig. 78). When the patient returned in 1937, the intraventricular block was again present and it persisted. The ventricular complexes of the standard leads are of the

kind ascribed to right bundle branch block, but the precordial leads indicate that the conduction defect was in the left branch of the His bundle instead of the right. The heart was in the vertical rather than in the horizontal position. The QRS complexes of Lead V_6 are diphasic and, as regards their general outline, of the sort obtained by leading directly from the surface of an infarct of the left ventricular wall when left branch block is present. But QRS deflections of this kind may occur in Lead V_6 merely because the transitional zone is shifted unusually far to the left. They are not sufficiently distinctive to be helpful in the diagnosis of infarction. A case of septal infarction plus left bundle branch block is described in the article to which we have already referred (see Fig. 82 of that article).

In conclusion, we may say that we feel certain that, in the long run, unipolar precordial leads will be found superior to precordial leads of other kinds. They are the best available substitute for unipolar direct leads from the anterior surfaces of the ventricles. They are not directly influenced by the potential variations of the extremities; this makes them valuable in the analysis of electrocardiographic patterns in the standard limb leads with which we have long been familiar.

We must add that many of the views expressed here must be regarded as tentative. There are still many problems to be solved. We do not know exactly what degree of correlation may exist between the electrocardiographic position and the anatomic position of the heart. We have, as yet, very little information as to the effect of the latter upon the precordial electrocardiogram. The factors that determine the location and breadth of the transitional zone are still obscure. It is desirable that the effects of preponderant hypertrophy of the right and of the left ventricle upon the form of the precordial deflections be studied experimentally. It is still impossible to diagnose the lesser grades of this condition with any certainty. We need to have a better idea as to what parts of the heart's surface play the most important role in determining the potential variations of the extremities and other points on the body distant from the heart. We must study more carefully the electrocardiographic changes produced by combinations of lesions, such as right ventricular hypertrophy and right bundle branch block, and by conduction defects which delay the activation of local regions of muscle, particularly in myocardial infarction ("arborization block"). We must determine more exactly what the different electrocardiographic patterns seen in infarction mean in terms of the size of the infarct, its location, and the character of the changes in the muscle involved.

We feel sure that the future will see a great increase in the use of precordial and other special leads, and that it will bring us far greater knowledge of the electrocardiogram than we now possess.

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TOXIC REACTIONS TO THE INTRAVENOUS INJECTION OF MERCURIAL DIURETICS

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ALTHOUGH it has been known for at least eleven years that sudden death may occur after intravenous injections of mercurial diuretics, it has been only within the past two years that widespread interest has arisen among physicians concerning these unfortunate accidents. In 1931, Wolf and Bongiorno[1] reported a case of sudden death of a 4-year-old child with nephrosis after the intravenous injection of 1 c.c. of salyrgan. In 1936, Cadbury[2] reported a fatality after the first injection of 0.6 c.c. of salyrgan into the jugular vein of a 5-year-old boy with nephritis. Collapse and death ensued within ten minutes. In addition, he cited instances of serious, nonfatal reactions to salyrgan in three adults with well-marked renal disease. The next year Greenwold and Jacobson[3] added two more cases of sudden death of children with nephrosis, one after 0.5 c.c., and the other after 1 c.c., of salyrgan, intravenously. In 1941, Tyson[4] observed one more fatal reaction in a 3-year-old nephrotic patient and a near fatality in a 27-year-old person with the same disease.

These papers, which appeared in a ten-year period, attracted little attention, probably because all of the fatalities occurred in very young children who were suffering from serious renal disease. However, in November, 1941, a letter was published in the *Journal of the American Medical Association*[5] citing four fatal reactions to mercupurin intravenously in patients with cardiac decompensation. The same cases were discussed in greater detail in a later communication.[6] At the same time a clinical study by Barker, Lindberg, and Thomas[7] added three more fatalities among cardiac patients and one in a 48-year-old patient with the nephrotic stage of chronic glomerulonephritis. In the last case, death occurred after the first injection. In all except one of these cases, death took place within five minutes after an intravenous injection of a mercurial diuretic (salyrgan or mercupurin).

The purpose of this communication is to add two more fatal reactions to mercupurin to the growing list, and, especially, to emphasize that nonfatal reactions of varying types and degrees of severity occur not uncommonly. The pathogenesis and the relation of these different types of nonfatal to fatal reactions will be discussed. No attempt has been

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Received for publication March 15, 1943.

made to survey the total number of reactions which have occurred at the Boston City Hospital; indeed, this is impossible, as will be evident. Nevertheless, in the past sixteen months, two fatal and nine alarming nonfatal reactions to such medication have come to our attention, some of which we have personally observed.

FATAL REACTIONS

The first fatal reaction occurred in a 24-year-old white woman with congenital pulmonary stenosis who had chronic cardiac failure. This patient had previously received a total of 164 c.c. of mercupurin intravenously over a period of eight months, with fair diuretic results. As her general cardiac status deteriorated, the response to mercupurin became less favorable. The dose was, therefore, gradually increased from 2 c.c. until she was receiving 3 c.c. of mercupurin three times a week. This maintained her weight quite constant. After each injection this patient was apprehensive, and had dyspnea, slight tachycardia, and orthopnea which lasted one to two minutes. Within one to two minuter after the final intravenous injection of 3 c.c., which was given at a time when the patient was extremely ill, she became very dyspneic and cyanotic, and died within a few minutes. Post-mortem examination showed no immediate cause of death, but confirmed the diagnosis of congenital pulmonary stenosis. Cardiac sclerosis of the liver was also found, together with the usual pathologic accompaniments of congestive heart failure.

The second fatality occurred in a 27-year-old white woman with nephrosis. She had received thirteen previous intravenous injections of mercupurin with no objective untoward reaction, but on each occasion she expressed great dislike for the injection because of an extremely unpleasant sensation which she could not describe. Within thirty seconds after the final intravenous injection of 2 c.c., which was given when the patient had improved sufficiently to be ambulatory, she became unconscious and rigid. She had three generalized tonic convulsions within the next two to three minutes. The pulse could not be felt at the wrist and there were no audible heart sounds. There was marked pallor of the face. Gasping respirations occurred a few times, but cardiac function could not be restored by injecting stimulants into the heart and giving artificial respiration. At post-mortem examination no immediate cause of death could be found. The kidneys showed the pathologic changes of chronic "nephrosis," and there was marked fibrosis of the thyroid gland. There were no other significant post-mortem abnormalities.

NONFATAL REACTIONS

These have varied in severity, and may be divided into immediate and delayed reactions. All of these reactions occurred in patients with edema caused by heart disease of various kinds.

A. *Immediate Reactions.*—

1. The most benign of the immediate reactions is entirely subjective. The patient dreads the injection because of an unpleasant sensation, with no objective disturbances of any kind. These patients have no objection to routine venepunctures or other intravenous medication. These untoward symptoms are not uncommon, but their exact frequency cannot be ascertained because they may not be called to the attention of the attending physician, or their import is not appreciated at the time.

2. Transitory dyspnea was noted in two cases within a few minutes after the intravenous injection of mercupurin.

The first patient was a 45-year-old white man with rheumatic heart disease, mitral stenosis, and aortic regurgitation, and moderate right- and left-sided failure. The first injection of 1 c.c. of mercupurin caused a transitory feeling of tightness in his chest. Two to five minutes after a rapid injection of 2 c.c., which was given two days later, he became very dyspneic but improved without treatment in a few minutes. Two subsequent injections of 1 and 2 c.c., diluted with 10 c.c. of saline, were given without reaction.

The second patient was a 71-year-old woman with coronary heart disease and moderate failure. One to three minutes after 2 c.c. of mercupurin were given intravenously she became very dyspneic, but improved without treatment a few minutes later. She had received mercupurin on previous hospital admissions without reaction.

3. A more alarming reaction consists of apprehension, substernal discomfort, slight increase in respiratory and pulse rate, and orthopnea.

This was observed in a 46-year-old white woman with hypertensive and rheumatic heart disease and moderate failure. Two to five minutes after 1.8 c.c. of mercupurin she became dyspneic and apprehensive and complained of substernal oppression. There was no change in blood pressure. The pulse rate rose to 100 per minute. Fifteen minutes later she was improved without treatment. This patient had received numerous previous injections without reaction; no subsequent injections were given.

4. Moderate collapse, cyanosis, and sweating were observed in two cases, with bradycardia in one and tachycardia in the other.

The first was a 33-year-old white man with rheumatic heart disease, mitral stenosis and regurgitation, aortic regurgitation, and auricular fibrillation, who was convalescing from cardiac decompensation. An initial injection of 2 c.c. of mercupurin was given without reaction. Several days later a second injection was followed in two to five minutes by pallor, cyanosis, and profuse sweating. The pulse rate was slow and regular at 50 per minute. An electrocardiogram which was taken twenty minutes later, when the patient was improved, showed auricular fibrillation with periods of complete heart block and a ventricular rate of 50.

The second patient was a 58-year-old white woman with hypertensive and coronary heart disease and moderate failure. Two to five minutes after 2 c.c. of mercupurin she became very apprehensive, dyspneic, and cyanotic, and perspired profusely. The pulse rate was rapid and the heart sounds were of poor quality. She responded to the administration of morphine and oxygen. Milder reactions had previously been noted after the administration of mercupurin intravenously.

It seems clear that these various immediate reactions are similar in nature. They differ only in degree.

B. *Delayed Reactions.*—The delayed reactions generally occur one to two hours after the injection.

1. Typical asthmatic attacks one to two hours after mercupurin administration were observed in two cases.

The first patient was a 69-year-old white man who was suffering from syphilitic and coronary heart disease, with slight right-sided failure and chronic bronchitis; he had previously received several injections of mercupurin without reaction. Two hours after the last injection of 2 c.c. of mercupurin he had a chill and became cyanotic and markedly dyspneic. On examination, both lungs were filled with high-pitched expiratory râles and wheezes. There had been no previous attacks of asthma. He responded to adrenalin in about thirty minutes.

The second patient was a 62-year-old man with hypertensive and coronary heart disease and congestive failure who developed dyspnea, with typical asthmatic breathing, about two hours after a third dose of 2 c.c. of mercupurin; the first two had been given without reaction. Recovery occurred before treatment was instituted.

2. Pulmonary demea developed one to two hours after the injection in two cases.

The first patient was a 22-year-old man with rheumatic fever, rheumatic heart disease, mitral stenosis, and cardiac decompensation, who received 2 c.c. of mercupurin intravenously for the first time. About one-half hour later he suddenly developed acute pulmonary edema, which responded promptly to routine therapy, consisting of morphine, oxygen, and tourniquets.

The second patient was a 37-year-old white woman with rheumatic heart disease, mitral and aortic stenosis and regurgitation, and moderate heart failure, who was given 2 c.c. of mercupurin intravenously. One hour later she had a chill, followed in twenty minutes by pulmonary edema. Recovery was prompt. Numerous previous injections had caused no symptoms.

DISCUSSION

Immediate Reactions (Fatal and Nonfatal). 1. *Clinical Considerations.*—The composite clinical picture of the fatal reaction, as constructed from our observations and from the descriptions in the literature, is characterized by a marked fall in blood pressure, either cardiac

arrest, cardiac irregularity, and/or marked bradycardia, cyanosis or marked pallor of the face, dyspnea with irregular, often gasping, respiration, unconsciousness, and, occasionally, convulsions. Generally, cardiac arrest occurs before respiratory paralysis, and death ensues within five minutes after the start of the injection.

Immediate nonfatal reactions occurred in many of the patients who ultimately died after the intravenous injection of a mercurial diuretic. This has already been mentioned as occurring in our two fatal cases. Wolf and Bongiorno's[1] patient had a febrile reaction to each injection of salyrgan. One week prior to death this patient developed the usual febrile response, plus a morbilliform rash. This subsided, and, one week later, 1 c.c. of salyrgan was given intravenously, with a fatal outcome within one minute. One of the patients reported by Barker, et al.,[7] had essentially a "fatal type" of reaction, with cardiac arrest, after the thirteenth injection of 2 c.c. of mercupurin, but recovered spontaneously ten minutes later. Four months later a similar reaction followed 2 c.c. of salyrgan, with death within two minutes. Similarly, in three of the four cases reported by Brown, et al.,[6] reactions to mercupurin were noted prior to the final fatal reaction.

In each instance, with the possible exception of Wolf and Bongiorno's case, previous reactions were of the immediate type, and, when multiple, the reactions always followed the same pattern in any one patient.

2. *Pathogenesis.*—The pathologic physiology of fatal reactions in man is not known. Post-mortem examinations have failed to disclose the cause of death.

However, the mechanism of the fatal and the nonfatal immediate reactions are probably basically similar, and differ only in degree.

Hyman[8] suggested that fatal reactions to mercupurin are nonspecific, and produce incoagulability of the blood, as does "speed shock," which may occur when any material is rapidly injected intravenously. The symptomatology of "speed shock," as described by Hirshfeld, et al.,[9, 10] is variable, but, generally within one minute after a rapid intravenous injection, salivation, vomiting, diarrhea, dyspnea, often with irregular respiration, muscle atony or muscle spasm, a fall in blood pressure, and bronchospasm may occur. There is no constancy about the appearance of any of these symptoms in experimental animals. It is stated that, when "speed shock" does occur, the blood is rendered incoagulable. However, the blood of one of our patients, taken about five minutes after death, clotted firmly and promptly, but did undergo apparently complete fibrinolysis about fifteen to thirty minutes later. According to the work of Skundina,[11] this spontaneous fibrinolysis is not specific for "speed shock" or mercurial intoxication, but is usually found in patients who die suddenly with severe shock from any cause.

Jackson[12] produced ventricular fibrillation and death in dogs within three to five minutes after the intravenous injection of 5 c.c. of a 2 per

cent solution of salyrgan. If both vagi were cut prior to the injection, death resulted from respiratory paralysis without ventricular fibrillation. Chastain and Mackie,[13] Barker, et al.,[7] DeGraff and Lehman,[14] and others, employing various mercurial injections in experimental animals, noted no difference after vagotomy, but otherwise obtained similar results. Whether the same mechanism pertains to man awaits further investigation. Clinical observations suggest that the mechanism is the same, at least in so far as the fact that the heart seems primarily involved. Essentially the same clinical picture is seen when cardiac patients die suddenly. We have watched two patients with myocardial infarcts die of ventricular fibrillation while an electrocardiographic recording was being made. These patients presented a picture that was almost identical to what has been described above, consisting of marked cyanosis, absence of the radial pulse and blood pressure, and whirring precordial noise without recognizable heart sounds. Gasping respirations continued for two to three minutes.

It has been suggested in the earlier reports that the reactions are anaphylactic in nature. There seems to be adequate evidence against this explanation of the type of reaction under discussion. First of all, the collapse which has been observed in all fatal reactions and in some of the nonfatal reactions has always been "cardiac collapse," i.e., acute forward failure, and not the peripheral vascular collapse which generally accompanies anaphylactic reactions. All of the *immediate* fatal and nonfatal reactions have occurred after *intravenous* injection of a mercurial.* In cases of nonfatal immediate reactions, subsequent intramuscular injections have caused no reaction.[6] On the other hand, patients who have shown definite allergic reactions, such as urticaria, rash, fever, etc., after intravenous injection of mercurials, showed the same reactions when the mercurial was administered intramuscularly, or in the form of a rectal suppository.[15, 16, 18] The fact that the early fatalities which were reported occurred after multiple, apparently asymptomatic injections outwardly seemed to favor anaphylaxis; the reasoning was that the preliminary injections sensitized the patient, thus setting the stage for the fatal reaction. However, at least three cases appear in the literature in which death followed the first injection.[2, 7, 19]

The suggestion that the mechanism is simply a toxic reaction to the mercury ion seems fairly well supported by laboratory and clinical observations. Salant and Kleitman,[20] in perfusion experiments with inorganic mercury salts, have produced marked disturbances in the rhythm of the turtle heart. They found that the time required to obtain toxic effects on the heart varied with the concentration of the mercury salt. "Delirium cordis" was produced with dilutions as high

*We have omitted from this review deaths reported after the use of older mercury preparations which caused symptoms typical of mercury poisoning because these were not immediate sudden deaths, and represent an entirely different syndrome. The case reported by Molnár,[17] in which death followed twenty to twenty-five minutes after the intraperitoneal injection of 2 c.c. of mercury, likewise does not come under the syndrome of sudden immediate death.

as 1:10,000,000. Similar results were obtained with the acetate, succinate, and benzoate of mercury, thus excluding the role of the anion. Their results with cats and dogs were similar to those of more recent studies on the toxicity of the organic mercurials,[7, 12-14] although they do not mention ventricular fibrillation, but speak of "delirium cordis."

Sollmann[21] states that mercury is rapidly removed from the blood stream, and stored especially in the kidneys and liver. From these depots traces of mercury may be mobilized for as long as six months. The chief channels for the excretion of mercury are the kidneys and the gastrointestinal tract. After a single dose, excretion begins within a few hours and may last for as long as eight days. After a series of injections, excretion of small amounts may persist intermittently for several months. Goodman and Gilman[22] essentially agree with this. DeGraff, et al.,[23] studying the effect of theophylline on the excretion of mercury in rabbits, showed that nearly 100 per cent of the mercury was excreted at the end of six hours. The preparations used were mercurin and salyrgan with and without theophylline, and the dose was 3.71 mg. of mercury in the salyrgan experiments and 3.8 mg. of mercury in the mercurin experiments. The possibility of cumulation in patients with impaired renal function, and, perhaps to less extent, in patients with prolonged circulation time, is not excluded, and may possibly account for the greater frequency of fatal reactions after multiple injections.

In summary, it may be said that toxic effects on the heart are possible with very low concentrations of mercury in the blood if these concentrations are maintained for a sufficiently long period of time. Cardiac failure and impaired renal function favor a higher concentration of mercury and tend to maintain that concentration for a longer period of time. The possible cumulation of mercury in the presence of cardiorenal disease may account for the greater incidence of serious reactions after multiple injections of mercurials.

Delayed Reactions.—The nonfatal delayed reactions may well be incidental to the physiologic effects consequent on the diuretic action of the drug. Swigert and Fitz[24] have shown that, in some patients, a transitory increase in plasma volume occurs after salyrgan is given; and Calvin, Decherd, and Herrmann[25] have also made this observation in two cases in which diuresis was delayed or failed to occur. This can account for pulmonary edema or bronchial congestion, with asthmatic type of respiration, in patients with little cardiac reserve. It is not unlikely that, in those who develop asthma, the cardiovascular disturbance is essentially the same as in the patients who develop pulmonary edema, for it is well known that, in paroxysmal nocturnal dyspnea, asthmatic breathing either may be absent or may dominate the picture. The occurrence of pulmonary edema after intravenous mercurial diuretic administration has been noted by several observers.[15, 24, 25]

In two of our patients, cyanosis and dyspnea followed a chill. In these cases the possibility exists that the chill was a nonspecific reaction, such as is occasionally seen after any type of intravenous therapy, and that this, in turn, so disturbed the cardiovascular system that pulmonary edema resulted. There is, however, evidence[1, 18, 26] that repeated chills may be specific reactions, for, in some cases, chills have recurred regularly after each injection of a mercurial diuretic.

In discussing this group, it is appropriate to mention the occasional case of mild digitalis intoxication which occurs in digitalized patients after marked diuresis. In our experience the symptoms have not been very troublesome, and have generally disappeared completely within twenty-four hours. Such cases are not common; more often, the accentuation of the digitalis effect may be manifested by slowing of the heart rate after a good diuretic response to the drug.

In our experience, elevation of blood nonprotein nitrogen after mercurial diuretics is rare, but does occur. The explanation of these rare elevations in nonprotein nitrogen is more likely to be found in the loss of electrolytes and water, resulting in dehydration, rather than in a nephrotoxic action of the mercury. Similar complications resulting from the pharmacologic action of mercurial diuretics are fully discussed by DeGraff and Nadler.[15]

PREVENTION OF REACTIONS

At present there is no known method of preventing fatal reactions. However, the following points are worth bearing in mind.

1. The incidence of fatal reactions is quite low. In this hospital, during a sixteen-month period, about 5,200 ampoules of mercupurin were issued, and, during this approximate period, two known fatalities occurred.

The incidence of nonfatal reactions is greater, for we have noted, during this same period, at least nine; five were of the immediate type and of sufficient severity to cause alarm to both the patient and the physician; and mild immediate reactions have occurred not uncommonly.

2. Most of the fatal reactions are preceded by nonfatal reactions which, if of the more serious immediate type, should serve as a warning, and, thereafter, mercurials should not be given except when other measures have failed, and then only with great caution; if feasible, they should be administered intramuscularly or in suppository form. Only three fatalities have been reported after the first injection of a mercurial diuretic. There is no evidence that dilution of the drug in 10 c.c. of water or normal saline protects against reactions, for these have been observed when such dilute solutions have been used,[19] and the experimental work of DeGraff, et al.,[14] offers evidence against any rationale for such dilution.

3. There is no indication that changing from one preparation to another is a safeguard against *fatal* reactions. However, nonfatal delayed

reactions may in some cases be specific for a given preparation. Thus, in the case reported by Fox, Gold, and Leon,[18] serious reactions, consisting of fever, erythema, paresthesias, and, occasionally, ulcerative stomatitis, followed the use of mercupurin intravenously or a mercurin suppository, but only very mild reactions occurred after salyrgan and inorganic mercurials.

4. Our experience here, and the experience of others as expressed in the literature, would indicate that the common drugs prescribed in heart failure, such as digitalis, ammonium chloride, nitrites, aminophylline, etc., have no effect on the toxicity of mercurial diuretics, nor does the type of heart or renal disease. Patients who are already very ill are perhaps more likely to succumb than those in a better state of health, for they are less able to stand the strain of a reaction. A relatively good state of health is, however, no protection against a fatal reaction, as is evident in our second case.

SUMMARY

Two fatal reactions to the intravenous administration of mercupurin, with post-mortem observations, are reported. Various nonfatal reactions to mercupurin are described and divided into the immediate and delayed types. The relation of the immediate type of nonfatal reaction to fatal reactions is stressed. The mechanism of the reactions to mercurial diuretics is discussed, and it is concluded that the fatal and the immediate nonfatal reactions probably result from a direct toxic effect of mercury on the heart, whereas the delayed nonfatal reactions are incidental to the diuretic action of the drug. These conclusions seem to be substantiated by experimental work on animals, as reported in the literature, and by our own clinical observations. At present there is no known way of preventing fatal reactions.

Since mercurial diruetic drugs are valuable therapeutic agents in the treatment of congestive heart failure, and since the frequency of severe or fatal reactions to their administration is low, the usefulness of these drugs outweighs their possible danger. They should, however, be administered only when clearly indicated, and the occurrence of danger signals, which have been discussed, warrants a complete reevaluation of the therapeutic regimen in any given case. It is well to remember that, at the present time, no fatalities have been reported after intramuscular injection of a mercurial diuretic, and that the diuretic response often compares favorably with that which results from intravenous injection.

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EXPERIMENTS WITH CALCULATED THERAPEUTIC AND TOXIC DOSES OF DIGITALIS

V. Comparative Effects of Toxic Doses of Digitalis and of Pitressin on the Electrocardiogram, Heart, and Brain*

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THE purpose of these studies was to ascertain whether repeated, large doses of the vasoconstrictor, pitressin, could induce changes in the electrocardiogram, in the myocardium, and in the brain which resembled those produced by toxic doses of digitalis.

LITERATURE

Various cardiovascular responses to posterior pituitary extracts have been studied since 1895, when Oliver and Schäfer[1] showed that their extracts were capable of producing a rise of the blood pressure and a slowing of the heart rate. Howell[2] and von Cyon[3] observed similar changes after posterior pituitary extracts had been administered to dogs and rabbits. Szymonowicz[4] described a slight decrease of the blood pressure and rise of the cardiac rate. Schäfer and Vincent[5] stated that pressor and depressor substances existed in their extracts. The pressor effect was accompanied by slowing of the heart rate. Garnier and Thaon[6] described a brief rise, then a fall, and, finally, a substantial rise of the arterial pressure of the rabbit after posterior pituitary extracts had been administered. Paukow[7] and Fühner[8] observed changes in blood pressure similar to those noted by Garnier and Thaon. Gruber[9] reported that vasopressin produced a rise of the blood pressure in all doses when injected intravenously into dogs anesthetized with chloretone; a fall of blood pressure occurred in unanesthetized dogs. Gruber and Kountz[10] stated that pitressin caused, first, a decrease of the heart rate during the primary rise of blood pressure, and then an acceleration of the heart rate during the fall in blood pressure; finally, the cardiac rate decreased during the prolonged rise of blood pressure. Goldenberg and Rothberger[11] observed a decrease of the blood pressure after the administration of pitressin to dogs. They considered that this reaction was the result of diminished cardiac output produced by the effects of coronary spasm on the myocardium.

Isolated arterial rings immersed in pituitary extracts were found to be decreased in caliber by de Bonis and Susanna[12] and by Pal.[13] On

Received for publication Feb. 28, 1942.

*Abridgment of portion of thesis submitted by Dr. Dearing to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Ph.D. in Medicine.

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the contrary, Cow[14] stated that rings of coronary arteries were sometimes constricted and sometimes dilated. Rischbieter[15] observed that the ear vessels of the rabbit constricted after the administration of pituitary extracts. Geiling, Herrick, and Essex[16] found that pressor fractions from the posterior lobe of the pituitary gland reduced the blood flow in the femoral artery and vein. They used the thermostromuhr to measure the volume of blood flow.

The effects of extracts of the posterior lobe of the pituitary on the coronary blood flow in isolated heart preparations have been studied by numerous investigators. Dale[17] found a diminution of the coronary blood flow, along with a decrease of the strength of cardiac contraction. Meyer[18] did not observe any significant change in the coronary blood flow. Rabe[19] reported that either a contraction or a dilatation occurred. Gunn[20] described a diminution of 70 per cent in the coronary blood flow. Gruber[21] stated that neutralized pituitary extracts caused coronary vasoconstriction, but that unneutralized commercial extracts caused vasodilatation. Gruber and Kountz[22] observed that pitressin in both alkaline and acid solutions produced vasoconstriction of the coronary vessels.

Morawitz and Zahn,[23] Bodo,[24] Rössler,[25] and Ross, Dreyer, and Stehle[26] stated that the coronary blood flow, as measured by the Morawitz cannula method, is diminished by posterior pituitary preparations.

Anrep and Stacey[27] and Häusler[28] showed that posterior pituitary extracts decrease the coronary blood flow as measured by the hot-wire anemometer.

The thermostromuhr has been used in recent years to measure the coronary blood flow after the administration of pitressin. Hochrein[29] observed an increase of the coronary blood flow, whereas Dietrich[30] and Essex, Wegria, Herrick, and Mann[31] described marked decreases. The latter authors showed that the blood flow may remain less than the control level as long as forty-five minutes.

Numerous electrocardiographic changes after the administration of posterior pituitary extracts have been described by Claude, Porak, and Routier,[32, 33] Hecht and Nadel,[34] Resnik and Geiling,[35] Gruber and Kountz,[36] Goldenberg and Rothberger,[11] and Dietrich.[30]

METHODS

These experiments were done on fifteen trained cats.

The pitressin (20 pressor units per cubic centimeter) was prepared by Parke, Davis and Company. Usually the extract was administered intravenously; occasionally the intramuscular route was used.

Electrocardiograms were made on each animal.[37] The tracings were made before the pitressin was injected and at various intervals after its administration. In some animals the tracings were made during the injection and at intervals of only a few seconds; in others the tracings were made every five minutes, ten minutes, or fifteen minutes. In the more prolonged experiments, electrocardiograms were taken hourly or daily.

TABLE I

CORRELATION OF THE DOSAGE OF PITRESSIN, THE TIME INTERVALS, AND THE HISTOLOGIC STUDIES OF THE MYOCARDIUM

DATE	TIME	DOSAGE OF PITRESSIN (C.C.)	MODE OF ADMINISTRATION	DURATION OF EXPERIMENT	HISTOLOGIC CHANGES: PAPILLARY MUSCLE AND LEFT VENTRICLE	INTERVENTRICULAR SEPTUM	RIGHT VENTRICLE	LEFT ATRIUM	RIGHT ATRIUM
5/ 3/38	9:00 A.M.	3	Intravenous	Died on 2nd day	Yes +++	Yes ++	Yes +	No	No
	2:00 P.M.	3	Intravenous						
5/18/38	8:20 P.M.	3	Intravenous	Died on 2nd day	Yes ++	Yes +±	Yes +	Yes ±	±?
	10:45 A.M.	3	Intravenous						
	1:45 P.M.	3	Intravenous						
	4:30 P.M.	2	Intravenous						
5/10/38	9:15 A.M.	3	Intravenous	Died late on 2nd day	Yes ++	Yes ++	Yes ±	No	No
	11:40 A.M.	2	Intravenous						
	1:30 P.M.	2	Intravenous						
	3:35 P.M.	3	Intravenous						
5/11/38	8:40 A.M.	3	Intravenous						
5/24/38	8:10 A.M.	3	Intravenous	Died on 3rd day	Yes ++	Yes +	No	No	No
	10:40 A.M.	3	Intravenous						
	2:20 P.M.	2	Intravenous						
5/25/38	8:15 A.M.	2	Intravenous						
	3:30 P.M.	2	Intravenous						
5/30/38	8:15 A.M.	3	Intravenous	Died on 4th day	Yes ++	Yes ++	No	No	No
	10:30 A.M.	3	Intravenous						
	3:20 P.M.	2	Intravenous						
5/31/38	10:15 A.M.	2	Intravenous						
5/11/38	9:40 A.M.	1.8	Intravenous	Died on 13th day	Yes ++++	Yes +++	Yes ++	±?	+
	11:45 A.M.	2	Intravenous						
	1:45 P.M.	3	Intravenous						
	2:15 P.M.	2	Intramuscular						
	4:00 P.M.	1.6	Intramuscular						
5/12/38	8:50 A.M.	3	Intravenous						
	11:15 A.M.	2.6	Intravenous						
	1:50 P.M.	3	Intravenous						
5/13/38	9:00 A.M.	3	Intravenous						
	11:00 A.M.	3	Intravenous						
5/18/38	12:00 M.	3	Intravenous						
6/27/38	8:10 A.M.	3	Intravenous	Killed on 5th day	No	No	No	No	No
	12:00 M.	2	Intravenous						
6/28/38	8:00 A.M.	2	Intravenous						
6/29/38	8:00 A.M.	3	Intravenous						
6/30/38	8:00 A.M.	2	Intravenous						
5/ 2/38	8:50 A.M.	2	Intravenous	Died on 5th day	No	No	No	No	No
	10:50 A.M.	2	Intramuscular						
	11:50 A.M.	2	Intramuscular						
	1:50 P.M.	1.6	Intravenous						
	4:30 P.M.	2	Intravenous						
5/ 3/38	8:50 A.M.	2	Intravenous						
	11:50 A.M.	2	Intravenous						
	1:45 P.M.	2	Intravenous						
	2:30 P.M.	2	Intramuscular						
	4:45 P.M.	2	Intravenous						
5/ 4/38	9:45 A.M.	2	Intravenous						
	2:15 P.M.	2	Intravenous						
	4:50 P.M.	2	Intravenous						
5/ 5/38	9:00 A.M.	3	Intramuscular						
	11:00 A.M.	2	Intramuscular						
	1:45 P.M.	2	Intramuscular						
	3:45 P.M.	2	Intramuscular						
	4:50 P.M.	2	Intramuscular						

DATE	TIME	DOSAGE OF PITRESSIN (C.C.)	MODE OF ADMINISTRATION	DURATION OF EXPERIMENT	HISTOLOGIC CHANGES: PAPILLARY MUSCLE AND LEFT VENTRICLE	HISTOLOGIC CHANGES: INTERVENTRICULAR SEPTUM	HISTOLOGIC CHANGES: RIGHT VENTRICLE	HISTOLOGIC CHANGES: LEFT ATRIUM	HISTOLOGIC CHANGES: RIGHT ATRIUM
4/25/38	8:30 A.M.	2	Intravenous	Killed on 8th day	No	No	No	No	No
	10:30 A.M.	2	Intravenous						
	2:30 P.M.	2	Intravenous						
	4:50 P.M.	2	Intravenous						
4/26/38	9:00 A.M.	2	Intravenous						
	1:45 P.M.	3	Intramuscular						
4/27/38	9:00 A.M.	2	Intramuscular						
	11:00 A.M.	2	Intramuscular						
	1:45 P.M.	3	Intramuscular						
	4:00 P.M.	3	Intramuscular						
4/28/38	8:30 A.M.	2	Intramuscular						
	10:30 A.M.	2	Intramuscular						
	12:30 P.M.	2	Intramuscular						
	2:30 P.M.	2	Intramuscular						
	4:30 P.M.	2	Intramuscular						
4/29/38	8:25 A.M.	2	Intravenous						
	10:30 A.M.	2	Intravenous						
	12:30 P.M.	2	Intramuscular						
4/30/38	8:00 A.M.	3	Intravenous						
6/19/38	8:00 A.M.	3	Intravenous	Killed on 10th day	±	±	No	No	No
6/20/38	8:00 A.M.	3	Intramuscular						
6/21/38	8:00 A.M.	3	Intramuscular						
6/23/38	8:00 A.M.	3	Intravenous						
6/13/38	10:00 A.M.	2.8	Intravenous	Killed on 16th day	No	No	No	No	No
	2:45 P.M.	3	Intravenous						
6/14/38	2:30 P.M.	2	Intravenous						
6/17/38	1:58 P.M.	1.5	Intravenous						
6/18/38	10:00 A.M.	2	Intramuscular						
6/20/38	8:00 A.M.	2	Intramuscular						
6/21/38	8:00 A.M.	2	Intramuscular						
6/22/38	11:00 A.M.	3	Intramuscular						
6/24/38	8:00 A.M.	3	Intramuscular						
6/25/38	9:40 A.M.	3	Intramuscular						
6/27/38	8:00 A.M.	2	Intramuscular						
6/19/38	10:20 A.M.	3	Intravenous	Killed on 10th day	No	No	No	No	No
	4:00 P.M.	3	Intravenous						
6/19/38	11:00 A.M.	0.1	Intravenous	Killed on 12th day	No	No	No	No	No
	1:30 P.M.	0.1	Intravenous						
	3:30 P.M.	0.1	Intravenous						
6/20/38	As on 6/19/38								
6/21/38	As on 6/19/38								
6/22/38	As on 6/19/38								
6/23/38	As on 6/19/38								
6/28/38	8:00 A.M.	3	Intravenous						
5/19/38	8:25 A.M.	3	Intravenous	Killed on 33rd day	No	No	No	No	No
	10:25 A.M.	3	Intravenous						
	12:10 P.M.	2	Intravenous						
	2:40 P.M.	2	Intravenous						
	4:30 P.M.	2	Intramuscular						
5/20/38	9:00 A.M.	3	Intravenous						
	2:20 P.M.	3	Intravenous						
5/23/38	9:15 A.M.	3	Intravenous						
	2:50 P.M.	3	Intravenous						
	4:30 P.M.	2	Intramuscular						
5/24/38	11:30 A.M.	3	Intramuscular						
	3:50 P.M.	2	Intravenous						
5/26/38	3:00 P.M.	3	Intramuscular						

TABLE I—CONT'D

DATE	TIME	DOSAGE OF PITRESSIN (C.C.)	MODE OF ADMINISTRATION	DURATION OF EXPERIMENT	HISTOLOGIC CHANGES				
					PAPILLARY MUSCLE AND LEFT VENTRICLE	INTERVENTRICULAR SEPTUM	RIGHT VENTRICLE	LEFT ATRIUM	RIGHT ATRIUM
4/ 5/38	8:50 A.M.	0.3	Intravenous	Killed on 10th day	No	No	No	No	No
	10:50 A.M.	0.3	Intravenous						
	12:50 P.M.	0.5	Intravenous						
	2:50 P.M.	0.6	Intravenous						
	4:50 P.M.	0.75	Intravenous						
4/ 6/38	8:10 A.M.	0.5	Intravenous						
	10:10 A.M.	0.75	Intravenous						
	12:10 P.M.	0.1	Intravenous						
	2:40 P.M.	1	Intramuscular						
	4:40 P.M.	1	Intravenous						
4/ 7/38	8:40 A.M.	1	Intravenous						
	10:40 A.M.	1	Intravenous						
	12:50 P.M.	1	Intramuscular						
	3:15 P.M.	1	Intramuscular						
4/ 8/38	8:30 A.M.	1	Intravenous						
	10:30 A.M.	1	Intravenous						
	3:20 P.M.	1	Intravenous						
4/12/38	8:50 A.M.	2	Intramuscular						
	2:00 P.M.	2	Intramuscular						

Notes were compiled on the reaction of each animal to every injection of pitressin.

Those animals which did not die spontaneously were killed, after various periods, in an ether or chloroform chamber. Necropsies were performed immediately. The brain, spinal cord, heart, stomach, duodenum, ileum, uterus, diaphragm, biceps, and musculature of the abdominal wall were prepared for microscopic study as described in a previous paper.[38]

The animals described in a previous paper[38] served as controls.

RESULTS

A. Anatomic Studies of the Myocardium After Repeated Injection of Large Doses of Pitressin.—Fifteen cats were used in these experiments on the effect of repeated, large doses of pitressin on the structure of the myocardium.

Anatomic changes were observed in the cardiac muscle of six of the fifteen animals. Table I illustrates the number of doses of pitressin, the size of each dose, the mode of administration of the preparation, the duration of the experiment from the first injection of pitressin to the death of the animal, and the result of the histologic study of the myocardium.

The myocardial lesions resembled those seen after toxic doses of digitalis had been given, although the lesions produced by digitalis tended to be more extensive than those produced by pitressin. The anatomic changes in the myocardium were focal in distribution, as we noted with the lesions produced by digitalis. The early, definite changes

consisted of degeneration of the myocardial fibers (Fig. 1). Hemorrhage was commonly found in the early myocardial lesions. Later, exudative cells entered the zone of myocardial degeneration. The histologic changes were most likely to be found in the papillary muscle and in the region just beneath the endocardium of the left ventricle.

No evidence of arteriosclerosis was seen in any of the cardiac arteries or arterioles. Small, macroscopic, reddish verrucae were noted on the mitral valves in some of the animals. Subendocardial hemorrhages were observed macroscopically in several animals. Small doses of pitressin did not produce demonstrable histologic damage in the myocardium.

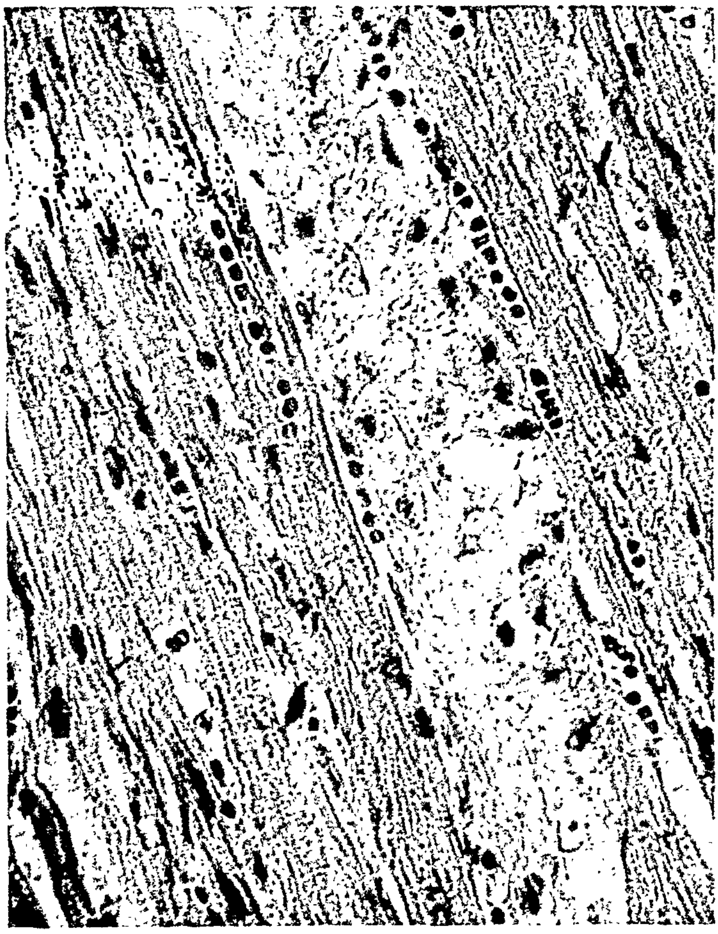

Fig. 1.—Degenerative changes in myocardial fibers after repeated injection of large doses of pitressin (×450).

The observation, made by many previous investigators, that second doses of pitressin may not produce any significant cardiovascular reaction, was confirmed. The fact that second doses of pitressin, injected too soon after the first dose, may not cause a significant decrease of the coronary flow may account for some, but perhaps not all, of our failures to bring about myocardial lesions in a number of animals.

The old animals were the only ones in which myocardial lesions developed. Myocardial changes were not found in several young cats.

B. Electrocardiographic Studies During the Repeated Administration of Large Doses of Pitressin.—The changes of the RS-T segment and T

wave which occurred during and after the administration of repeated doses of pitressin were as follows: (1) decrease of the height of the T wave in one or more leads; (2) increase of the height of the T wave in one or more leads; (3) simple inversion of the T wave in one or more leads; (4) depression of the RS-T segment in one or more leads; (5) elevation of the RS-T segment in one or more leads (not of the plateau type); (6) cove-plane, negative T_2 and T_3, associated with a positive T_1; (7) negative T_1 and T_2, associated with a positive T_3.

All the animals at one time or another showed changes in the height of the T waves or simple inversion of the T wave in one or more leads. Elevation of the RS-T segment (similar to that shown in Fig. 1*d* of the second paper in this series)[37] frequently was seen immediately after the pitressin had been injected; this elevation, however, did not persist long. The plateau type of elevation of the RS-T segment which occurred after administration of toxic doses of digitalis was not observed in the animals which received pitressin.

Depression of the RS-T segment (Fig. 2) was observed in a number of the animals. This pattern was striking in four cats.

The cove-plane, negative T_2 and T_3 pattern (Fig. 3) was found in two cats; both of these animals had degenerative lesions in the myocardium. One cat in which myocardial lesions developed did not show any significant changes in the RS-T segment or T wave in any of the electrocardiograms which were made each day.

Numerous other electrocardiographic changes were noted: profound sinus bradycardia, sinus tachycardia, bigeminy, ventricular premature contractions, complete heart block, ventricular tachycardia, and ventricular fibrillation. These changes after the administration of pitressin have been described by numerous previous investigators and do not need to be elaborated on.

TABLE II

CORRELATION OF THE DOSAGE OF PITRESSIN, THE TIME INTERVAL, AND THE HISTOLOGIC STUDIES ON THE CENTRAL NERVOUS SYSTEM*

DURATION OF EXPERIMENT	HISTOLOGIC CHANGES			
	CEREBRUM	CEREBELLUM	PONS	SPINAL CORD
Died on 2nd day	–	–	–	–
Died on 2nd day	–	–	–	–
Died late on 2nd day	Yes + +	No	Yes ±	No
Died on 3rd day	–	–	–	–
Died on 4th day	Yes + +	Yes +	Yes ±	No
Died on 13th day	–	–	–	–
Killed on 5th day	No	No	No	No
Died on 5th day	No	No	No	No
Killed on 8th day	No	No	No	No
Killed on 10th day	–	–	–	–
Killed on 16th day	No	No	No	No
Killed on 10th day	No	No	No	No
Killed on 12th day	No	No	No	No
Killed on 33rd day	No	No	No	No
Killed on 10th day	No	No	No	No

*For date, time, dose, and mode of administration, see Table I.

C. Anatomic Studies of the Central Nervous System After Repeated Injection of Large Doses of Pitressin.—Two of the six animals in which myocardial lesions were found after repeated injection of large doses of pitressin were suitable for microscopic examination of the brain. The

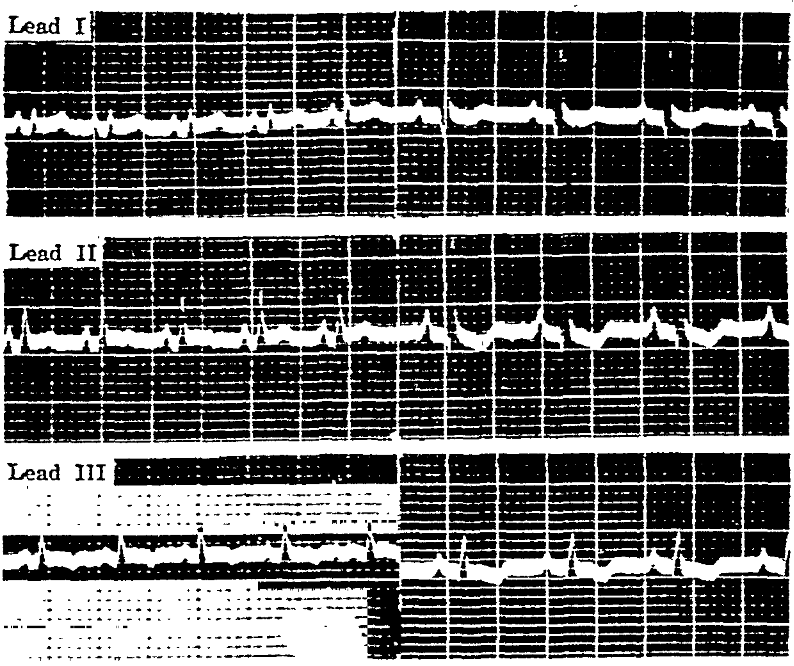

Fig. 2.—On the left, control electrocardiogram; on the right, depression of the RS-T segments after repeated injection of large doses of pitressin.

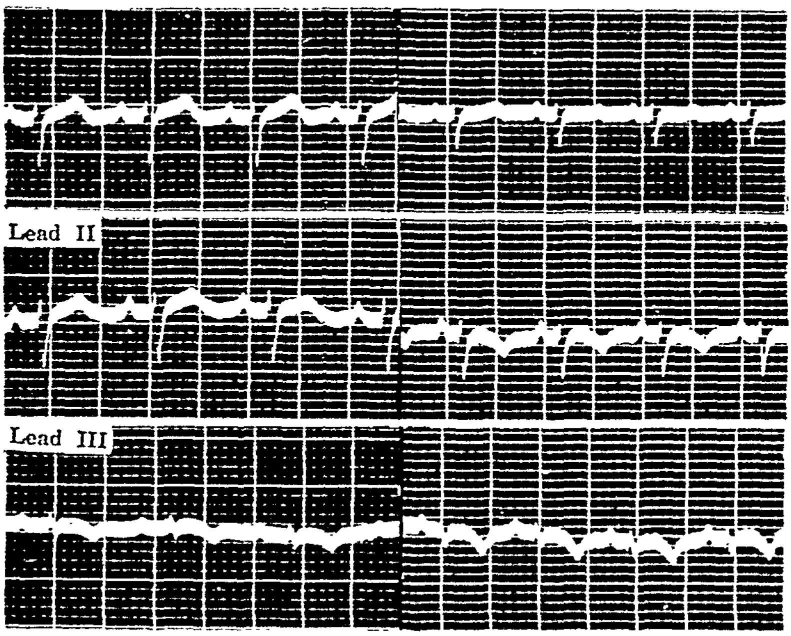

Fig. 3.—On the left, control electrocardiogram; on the right, cove-plane, negative T_2 and T_3 after repeated injection of large doses of pitressin.

brain and spinal cord of these two animals were removed immediately after spontaneous death. Table II illustrates the distribution of the lesions. The cerebral cortex was the most vulnerable. No changes were found in the cells of the spinal cord.

The brain and spinal cord of the remaining eights animals (Table II) were free from evidence of significant cellular lesions.

Fig. 4 illustrates the degeneration which was seen in the pyramidal cells of the cerebral cortex after repeated injection of doses of pitressin. The cortical cells after the administration of pitressin showed swelling, vacuolization, degeneration (necrosis), and pyknosis. These cellular changes resembled those that occurred after the administration of toxic doses of digitalis. However, the cortical lesions were much less extensive than some of those which were observed after toxic doses of digitalis had been administered.

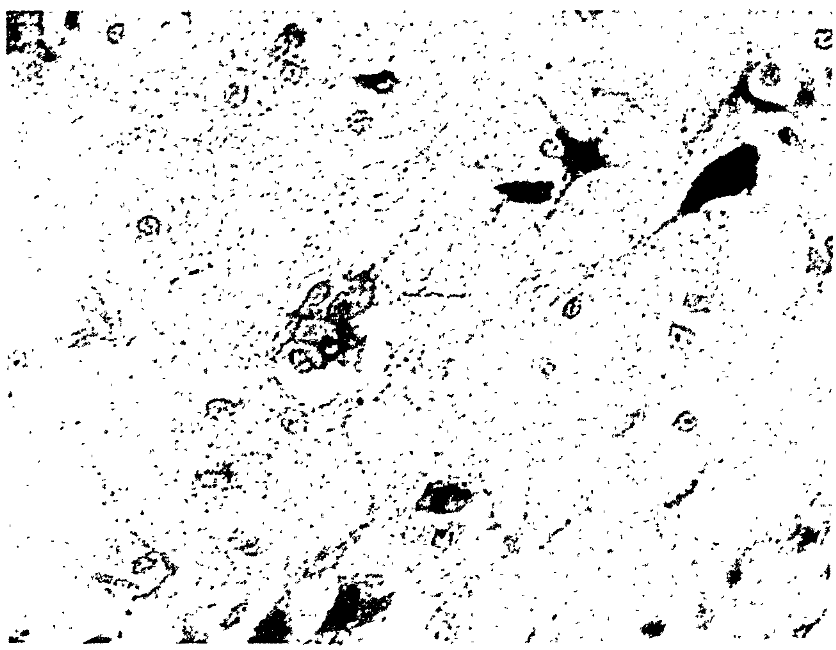

Fig. 4.—Degenerative changes in pyramidal cells of the cerebral cortex after repeated injection of large doses of pitressin (×450).

D. Macroscopic and Microscopic Changes in the Stomach After Repeated Injection of Large Doses of Pitressin.—These observations are confirmatory of those reported by Dodds, Noble, and Smith[39] and Dodds, Noble, Scarff, and Williams.[40]

In our studies, changes in the stomach were produced by repeated, large doses of pitressin. Macroscopically, the gastric mucosa of the fundus and upper portion of the pylorus was eroded by numerous ulcers. The mucous membrane of the stomach was either red from hemorrhage or black from the action of acid on the extravascular hemoglobin.

Microscopically, the mucosa of the stomach showed varying degrees of degeneration of the fundic cells. Hemorrhage was a prominent feature in these lesions. The gastric smooth muscle was unchanged in the animals studied in our experiment.

The mucosa of the duodenum was entirely normal, both macroscopically and microscopically, even when the gastric lesions were extensive.

E. Signs Observed in the Cats After Injection of Large Doses of Pitressin.—An initial intravenous dose of 3 c.c. of pitressin caused profound bradycardia and, frequently, brief respiratory arrest. Paling of the oral mucosa, panting respirations, and ataxia soon appeared. Vomiting, urination, and defecation often occurred. These effects have been described by many previous workers. Recovery of the animal was gradual.

A second dose of pitressin, given soon after the initial dose, did not produce those changes, or, if they did occur, they were mild.

When the doses of pitressin were properly spaced, there was a recurrence of the foregoing effects each time the extract was administered intravenously.

After two or three doses of pitressin had been injected on the first day, the animals became very hungry and consumed large quantities of meat. A mucoid, diarrheal discharge often appeared at the end of the first day of treatment with one, two, or three large doses of pitressin.

Small doses of pitressin (0.1 c.c.) produced little external change in the animal. Bradycardia could be detected by palpation of the heartbeat or by the electrocardiogram.

The older the animal, the more striking were the untoward physical signs after the injection of a large dose of pitressin. Young animals tolerate large doses of pitressin better than the old ones.

COMMENT

The myocardial lesions are not easy to produce with repeated doses of pitressin. The dose of pitressin must be large, the time interval between succeeding injections must be optimal, and the animal must be old.

Doses of pitressin which are administered too soon after the initial injection are likely to produce little measurable change in the cardiovascular system. The coronary blood flow, in particular, may not be decreased by these repeated injections of pitressin, a fact known to Dale[17] in his early experiments with pituitary extracts. Furthermore, the decrease of coronary blood flow after administration of pitressin, although pronounced, is not sustained for a period longer than forty-five minutes (Essex, Wegria, Herrick, and Mann[31]). Therefore, if our assumption is correct, that the myocardial lesions in our experiment on the effect of pitressin are related to the decrease of the coronary blood flow, the experimental conditions must be optimal in order to attain repeated, sustained diminutions of the coronary blood flow.

We wish to avoid an error in the interpretation of our experiments by stating that it does not necessarily follow that the myocardial lesions produced by digitalis are induced by vasoconstriction in the coronary arteries just because pitressin decreased the coronary blood flow and

produced myocardial lesions which resemble those seen after the administration of toxic doses of digitalis.

SUMMARY

Histologic changes were observed in the myocardium after the repeated injection of large doses of pitressin. The myocardial lesions resembled those which occurred after the administration of toxic doses of digitalis. They were focal in distribution and were most prominent in the subendocardial layer of the left ventricular musculature.

The following is a summary of the changes in the RS-T segment and T wave after large doses of pitressin: (1) decrease or increase of the height of the T wave; (2) elevation of the RS-T segment (not of the plateau type) in one or more leads; (3) simple inversion of the T wave in one or more leads; (4) depression of the RS-T segment in one or more leads; (5) cove-plane, negative T_2 and T_3; and (6) cove-plane, negative T_1 and T_2.

Cellular degeneration was observed in the cerebral cortex after the repeated injection of large doses of pitressin.

Myocardial and cerebral lesions were not observed in all the animals which received large doses of pitressin.

Myocardial lesions were produced in the older, but not the younger, animals.

Gastric lesions were observed after the injection of large doses of pitressin. This confirms the observation of Dodds and his associates.

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EXPERIMENTS WITH CALCULATED THERAPEUTIC AND TOXIC DOSES OF DIGITALIS

VI. Comparative Effects of Toxic Doses of Digitalis and of Prolonged Deprivation of Oxygen on the Electrocardiogram, Heart, and Brain*

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The purpose of this investigation was threefold: (1) to ascertain whether prolonged deprivation of oxygen would produce electrocardiographic changes which resembled these induced by toxic doses of digitalis; (2) to ascertain whether prolonged deprivation of oxygen was capable of producing histologic changes in the myocardium similar to those observed after the administration of toxic doses of digitalis; (3) to find out whether prolonged deprivation of oxygen and toxic doses of digitalis produced similar cellular alterations in the central nervous system.§

LITERATURE

The literature on deprivation of oxygen is immense. Much of it, although extremely interesting, is not strictly relevant to our problem. The basic contributions dealing with the effects of deprivation of oxygen on the electrocardiogram, the cellular structure of the myocardium, and the central nervous system will be mentioned.

Let us consider first the pertinent publications which describe changes in the RS-T segment and the T wave in the electrocardiogram after systemic deprivation of oxygen. Greene and Gilbert[1] reported a decrease of the amplitude of the T wave in the early stages (precrises) of deprivation of oxygen produced in young men during rebreathing experiments; sometimes the T wave was diphasic or negative near the stage of circulatory crisis. Greene and Gilbert[2] made similar observations on dogs. Miki[3] described the "church-spire" T wave of abnormal height in asphyxia. Kountz and Gruber[4] reported that a "high branching T wave" occurred in dogs which were connected with a rebreathing apparatus. This change in the T wave was observed when the oxygen saturation of the blood fell to less than 50 per cent of normal. These authors concluded that the high, branching T wave of coronary occlusion was due to anoxemia. Kountz and Hammouda[5] described

Received for publication Feb. 28, 1943.

*Abridgment of portion of thesis submitted by Dr. Dearing to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Ph.D. in Medicine.

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§The authors wish to express their appreciation to Dr. Walter M. Boothby for his aid in working out the technique.

changes in the RS-T segment and T wave when the right or left coronary artery in the canine heart-lung preparation was perfused with asphyxial blood. These authors concluded that the changes in the R-T segment after coronary occlusion were due to a high concentration of locally produced metabolites. Rothschild and Kissin[6] induced anoxemia in thirty-eight persons with a rebreathing apparatus. The electrocardiograms of ten of these showed a downward deviation of the S-T segment; one person had an upward deviation of the segment. An average of 7.9 per cent oxygen in the inspired air caused S-T changes in the controls, whereas an average of 8.4 per cent produced S-T deviations in the patients with angina pectoris.

Katz and Hamburger[7] reported a decrease in the height of the T wave and a depression of the S-T segment in studies on twenty normal persons who breathed air in which the oxygen was diminished gradually to 7 volumes per cent. Dietrich and Schwiegk[8] described in man, during deprivation of oxygen (8 per cent in inhaled air) a depression of $RS\text{-}T_1$ and $RS\text{-}T_2$, a negative T_2 and T_3, and an elevation of $RS\text{-}T_2$ and $RS\text{-}T_3$, associated with a depression of $RS\text{-}T_1$. Dietrich[9] observed, in dogs, flattening of the T wave, inversion of the T wave, or depression of the S-T segment. He showed that these electrocardiographic changes occurred when the oxygen in the inspired air ranged from 6 to 9 per cent and when the coronary blood flow, as measured by the Rein thermostromuhr, was increased considerably. Cluzet, Piéry, Ponthus, and Milhaud[10] described an elevation of the T wave in dogs in a low pressure chamber. Tigges[11] observed a flattening of the T wave in normal persons who were subjected to hypoxemia. Larsen[12] administered 9 per cent oxygen to ninety persons, in some of whom he found a depression of the S-T segment, flattening of the T wave, and inversion of the T waves. Borgard[13] reported flattening of the T waves, with a transition to negative T waves; finally, the T wave became high and spiked. These studies were done on animals at low atmospheric pressures. Levy, Barach, and Bruenn[14] and Levy, Bruenn, and Russell[15] described a flattening of the T wave and occasional depression of the RS-T segment in persons who inhaled 10 per cent oxygen and 90 per cent nitrogen. May[16] made similar observations on normal persons.

Binet, Strumza, and Ordóñez[17] observed in dogs that a negative T_2 occurred when 7.36 per cent oxygen was inhaled, and an elevation of the R-T segment, along with a tall T wave, appeared when 2.41 or 2.89 per cent oxygen was administered. Scott, Leslie, and Mulinos[18, 19] subjected cats to atmospheres containing 10 per cent oxygen both before and after ligation of the left branch of the anterior descending coronary artery. The RS-T segment did not deviate from its isoelectric position with anoxemia preoperatively. After the coronary artery had been ligated, the RS-T segment was deviated upward; in time, the RS-T segment returned to the isoelectric position, even though the infarct persisted.

When the animals then were subjected to anoxemia, the RS-T segment assumed the deviation pattern which occurred just after the coronary artery had been ligated. Levy, Bruenn, and Williams[20] stated that, among patients suffering from angina pectoris and coronary sclerosis, changes in the RS-T segment and the T wave developed after the administration of digitalis (1.5 Gm. in four days). These changes resembled those caused by anoxemia.[14, 15] On the fifth day, anoxemia was produced in these digitalized patients; it was found that the deviation of the RS-T segment diminished by 40 per cent, and the interval between the production of anoxemia and the time of appearance of the pain was shortened 9 per cent. The latter observation agrees with the contention of Gilbert and Fenn[21] that digitalis increases the susceptibility to pain of patients suffering from angina pectoris. Gold, Otto, Kwit, and Satchwell,[22] on the contrary, stated that the likelihood that digitalis will produce angina is negligible.

Concerning the effects of systemic anoxia on the anatomic structure of the heart, several references were found in the literature. Schrötter[23] observed fatty degeneration in the myocardiums of guinea pigs which were subjected to low atmospheric pressures (230 mm. Hg) for forty hours. Campbell[24] also noted fatty changes in the myocardiums of cats, rabbits, calves, and mice after they had been exposed for a long time to low oxygen pressures. Luft[25] observed necrosis in the papillary muscle and in the left ventricular wall of the hearts of guinea pigs which had been subjected to low pressures (230 to 300 mm. Hg for 120 to 180 hours). For the sake of completeness, it may be worth while to mention that Büchner[26] produced necrosis of the myocardium in anemic, exercised rabbits, and that Liebmann,[27] Herzog,[28] Gey,[29] Gürich,[30] Tesseraux,[31] Kroetz,[32] Nagel,[33] and many others have described myocardial degeneration in man after poisoning by illuminating gas. Although the myocardial lesions produced by either coronary occlusion in man or coronary ligation in animals are too familiar to warrant comment, it might be of interest to point out that Tennant, Grayzel, Sutherland, and Stringer[34] did not observe anatomic changes in the myocardium until eight hours or more after coronary ligation. Karsner and Dwyer[35] described histologic changes twelve hours after permanent ligation of the coronary artery.

Some of the major contributions on the effects of deprivation of oxygen on the central nervous system will now be reviewed. Deprivation of oxygen has been produced in the central nervous system by temporary ligation of blood vessels, by the use of low pressure chambers, and by the inhalation of air of low oxygen content. de Buck and de Moor,[36] Mott,[37, 38] Hill and Mott,[39] Gomez and Pike,[40] and Gildea and Cobb[41] described cellular changes of the central nervous system after ligation of blood vessels. The changes in the nerve cells consisted of chromatol-

ysis, swelling of the cells, shrinkage of the cells, vacuolization of the cytoplasm, neuronophagia, and complete disintegration of the cells. Gildea and Cobb described foci of necrosis in the brains of their cats after temporary ligation of the cerebral vessels; they found that ten minutes of cerebral ischemia was sufficient to damage cortical cells permanently. Martin, Loevenhart, and Bunting[42] exposed rabbits to low oxygen tension (average oxygen percentage = 7.21 to 7.98) for twelve to 231 hours. They did not find any anatomic changes in the brain or spinal cord. Ford[43] asphyxiated cats and kittens by washing the air from a bell jar with nitrogen; then the animals were resuscitated and finally killed. No lesions were found in the brain. Büchner and Luft[44] described degenerative changes in the brains of guinea pigs which were subjected to low atmospheric pressures (250 to 300 mm. Hg) from 103 to 133½ hours.

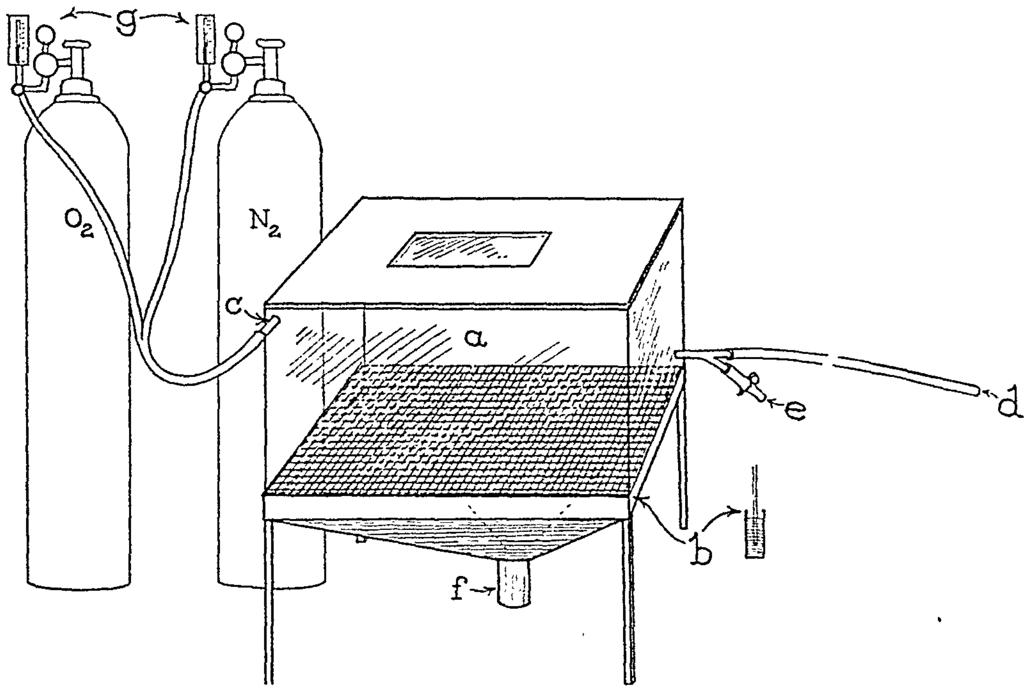

Fig. 1.—Diagram illustrating the apparatus used to attain low percentages of oxygen over long periods (days). *a*, Water-sealed chamber with wire cage floor; *b*, cross section showing the structure of the water-sealed border of the chamber; *c*, tube through which the gas mixture flowed into the chamber; *d*, tube, 6 feet (183 cm.) long, through which the gas mixture flowed from the chamber; *e*, side tube through which samples of gas were collected; *f*, sealed glass jar in which urine was collected; *g*, Heidbrink flowmeters connected to the oxygen and nitrogen tanks.

METHODS

Six cats were used in these studies on deprivation of oxygen. The animals were placed in a large, water-sealed chamber (Fig. 1), and breathed oxygen at low concentrations for several days. The desired concentration of oxygen was attained and maintained by allowing mixtures of oxygen and nitrogen to flow continuously into the upper portion of one end of the chamber and to flow out through the lower portion of the opposite end of the chamber. Influx of atmospheric air into the chamber was prevented by attaching a rubber tube, 6 feet (183 cm.) long and of small caliber, to the outflow opening.

The percentage of oxygen in the chamber was adjusted by controlling the rate of inflow of the nitrogen and oxygen through calibrated flowmeters attached to each gas tank. For example, if the nitrogen flowed at the rate of 9.5 liters per minute and the oxygen at 0.5 liters per minute, then the proportion of oxygen entering the chamber would be approximately 5 per cent ($\frac{0.5}{9.5 + 0.5} = 0.05$ or 5 per cent). These calculations permitted one to estimate quickly the percentage of oxygen at any moment during the experiment.

Samples of gas were collected at various intervals through a side tube placed near the outflow opening of the chamber. The percentages of oxygen and carbon dioxide were ascertained in these samples with the Haldane gas analyzer. The percentages of oxygen as calculated from the rates of flow of nitrogen and oxygen through the flowmeters agreed fairly well with those ascertained by actual analysis. The carbon dioxide was prevented from accumulating by maintaining a fairly rapid flow of nitrogen and oxygen through the chamber; therefore, absorption of the carbon dioxide with soda lime was not necessary. The content of carbon dioxide in the chamber varied from 0.2 to 0.6 per cent.

The cats lay on the right side while electrocardiograms were made at various intervals throughout the course of the experiment. The electrocardiographic lead wires traversed the outflow tube described previously.

The cats were removed from the chamber for a short time each morning to permit cleaning of the chamber, feeding of the animals, and readjustment of the electrocardiographic electrodes on their extremities. The electrocardiograms were taken as described elsewhere.[45]

Notes were made on the appearance and behavior of the animals while they inhaled the low-oxygen gas mixture.

The animals which did not die spontaneously were killed in an ether or chloroform chamber after they had inhaled the low-oxygen mixtures for three to eight days. The heart, brain, spinal cord, stomach, duodenum, ileum, uterus, biceps, diaphragm, and abdominal musculature were prepared for microscopic study in accordance with the procedure described in a previous paper.[46]

The control animals for the microscopic studies were the same as those described elsewhere.[46]

TABLE I

CORRELATION OF DURATION OF SYSTEMIC DEPRIVATION OF OXYGEN AND HISTOLOGIC STUDIES OF THE MYOCARDIUM

AVERAGE OXYGEN, PER CENT	MINIMAL OXYGEN, PER CENT	DURATION OF EXPERIMENT	HISTOLOGIC CHANGES					REMARKS
			PAPILLARY MUSCLE AND LEFT VENTRICLE	INTERVENTRICULAR SEPTUM	RIGHT VENTRICLE	LEFT ATRIUM	RIGHT ATRIUM	
4.43	4.43	1½ hours	No	No	No	No	No	Died
4.54	4.36	3 days	Yes ++++	Yes ++++	Yes ++	Yes +	Yes +	Extensive lesions
4.82	3.54	4 days	Yes ++	Yes ++	Yes +	?	?	Extensive lesions
5.29	4.36	4 days	Yes +	Yes +	Yes +	?	±	Extensive lesions
4.56	4.58	5 days	Yes +++	Yes ++	Yes +	Yes +	Yes +	Moderately extensive lesion
4.71	4.36	8 days	Yes +	Yes +	Yes ±	No	No	Few lesions

RESULTS

A. Anatomic Studies of the Myocardium After Prolonged Systemic Deprivation of Oxygen.—It will be recalled that the myocardiums of the control animals did not reveal any evidence of degenerative changes.

Table I indicates the effects of prolonged systemic deprivation of oxygen on the myocardium in our experimental animals. There were no changes in the myocardium of the animal which died one and a half hours after the inhalation of low concentrations of oxygen, whereas the five animals which survived three or more days in the low-oxygen gas mixture exhibited varying degrees of histologic change in the myocardium.

Fig. 2.—Degenerative changes in the myocardium after prolonged systemic deprivation of oxygen (×450).

The anatomic lesions produced in the myocardium after prolonged exposure to low-oxygen tensions differed very little from those which were seen after the injection of toxic doses of digitalis (compare Fig. 2 with Fig. 1 of the first paper of this series).[46] The lesions produced by digitalis were, as a rule, more extensive than those that occurred after deprivation of oxygen. The earliest definite and obvious change in the myocardium after prolonged anoxia was degeneration of the muscle fibers in localized zones (Fig. 2). In time, cellular degeneration, plus exudative cells, was present in the myocardium. These histologic changes

were apparently not different from those produced by the administration of digitalis or pitressin, coronary ligation, and so forth.

The cellular changes were most prominent and extensive in the papillary muscle, the left ventricular wall, and the interventricular septal wall. Except in two animals, the atrial and auricular anatomic changes were either absent or difficult to recognize.

The old animals died sooner and showed more extensive myocardial lesions than the young ones. For example, an old cat died spontaneously after three days of deprivation of oxygen, and its heart contained extensive degenerative changes, while a young adult cat lived for eight days at low oxygen tensions; it was killed on the eighth day, and its heart showed only a few degenerative lesions. This difference of sensitivity to deprivation of oxygen was not because of arteriosclerosis in the older animal, for no evidence of this disease was observed in the coronary arteries or arterioles of any of our experimental animals.

TABLE II

CORRELATION OF DURATION OF SYSTEMIC DEPRIVATION OF OXYGEN, HISTOLOGIC STUDIES OF THE MYOCARDIUM, AND THE MOST PROMINENT CHANGE IN RS-T SEGMENT AND T WAVE OBSERVED DURING THE EXPERIMENT

AVERAGE OXYGEN, PER CENT	MINIMAL OXYGEN, PER CENT	DURATION OF EXPERIMENT	HISTOLOGIC CHANGE IN MYOCARDIUM	MOST PROMINENT CHANGE OF RS-T SEGMENT AND T WAVE OBSERVED
4.43	4.43	1½ hours	No	Negative T_1
4.54	4.36	3 days	Yes	Cove-plane, negative T_2 and T_3; T_1 flattened but positive
4.82	3.54	4 days	Yes	Depression RS-T_1, RS-T_2 and RS-T_3; finally cove-plane negative T_2 and T_3
4.86	4.58	5 days	Yes	Depression RS-T_1, RS-T_2 and RS-T_3; finally cove-plane negative T_2 and T_3
4.71	4.36	8 days	Yes	Depression RS-T_1, RS-T_2 and RS-T_3

B. Electrocardiographic Studies During Prolonged Systemic Deprivation of Oxygen.—The changes in the RS-T segment and T wave observed after deprivation of oxygen (Table II) were as follows: (1) decrease in the height of the T wave in one or more leads, usually in all three leads; (2) increase in the height of the T wave in one or more leads; (3) inversion of the T wave in one, two, or three leads; (4) depression of the RS-T segment in one or more leads; (5) cove-plane, negative T_2 and T_3; (6) negative T_1 and positive T_2.

The RS-T segment was not elevated significantly (plateau type) in any of the electrocardiograms which were made while the animals were inhaling low-oxygen gas mixtures. It is not known whether the segments would have become elevated if the animals had been permitted to remain out of the low-oxygen chamber for a day or so after myocardial lesions had developed.

The succession of electrocardiographic changes was usually initiated by decreases in the height of the T waves, and sometimes by a negative

T_3; then either tall T waves or simply inverted T waves in one or more leads were observed; depression of the RS-T segments, with diphasic T waves in one or more leads (Fig. 3), was noted to precede or follow the tall T waves or the simply inverted T waves; finally, cove-plane,

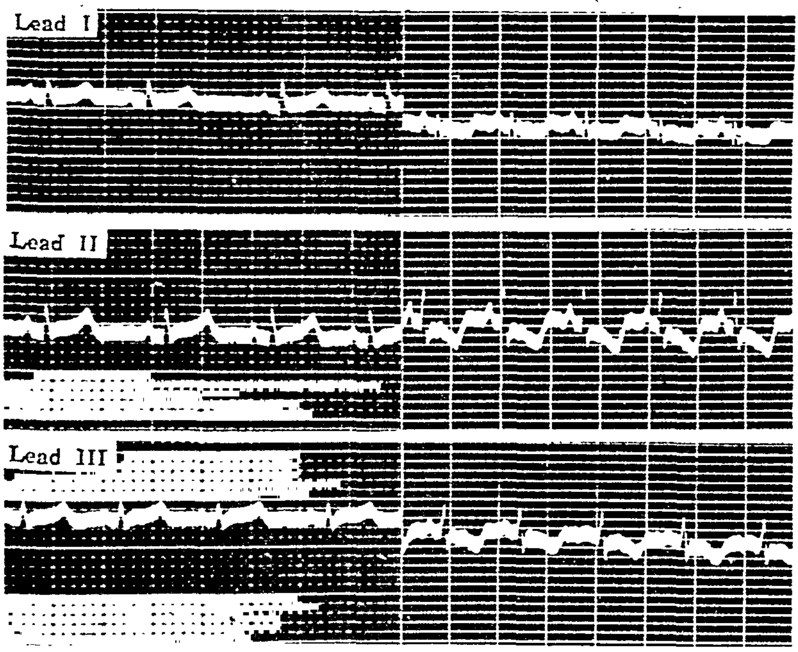

Fig. 3.—On the left, control electrocardiogram; on the right, depression of the RS-T segment after systemic deprivation of oxygen.

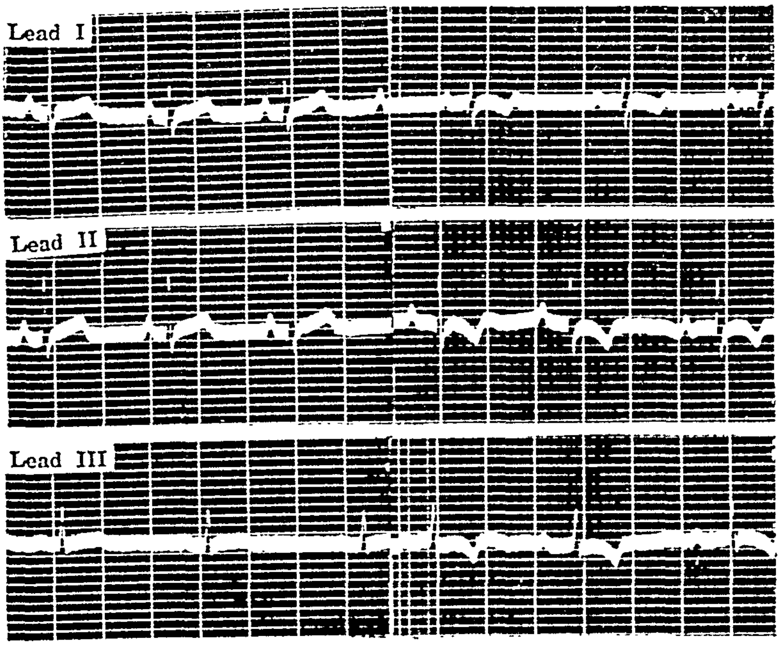

Fig. 4.—On the left, control electrocardiogram; on the right, cove-plane, negative T_2 and T_3 after prolonged deprivation of oxygen. Myocardial lesions were associated with this pattern.

negative T_2 and T_3, with flattened T_1 and diphasic T_1, preceded by a depressed RS-T_1 segment, were observed (Fig. 4). When the animals were permitted to breathe atmospheric air, the foregoing electrocardiographic changes were altered promptly or reverted to the normal pattern.

Many other electrocardiographic changes were observed during the various grades of anoxia: sinus tachycardia, sinus bradycardia, prolongation of the Q-T interval, heart block, decreased height of the QRS complex, flattening of the P wave, and so forth.

C. Anatomic Studies of the Brain and Spinal Cord After Prolonged Systemic Deprivation of Oxygen.—The central nervous systems of only three of our six experimental animals were examined microscopically (Table III). The cerebral cortex (frontal, motor, and visual), the cerebellum, the pons, and the spinal cord (cervical, thoracic, and lumbar) were the portions of the nervous system studied. The cerebral cortex was the most vulnerable to deprivation of oxygen. Degenerative lesions were observed in the cortices of all three animals. The cerebellum of one animal showed a few pyknotic and vacuolated cells. The pons in two animals contained scattered pyknotic and vacuolated cells. No evidence of degeneration was seen in any of the cells in the spinal cord.

TABLE III

CORRELATION OF DURATION OF SYSTEMIC DEPRIVATION OF OXYGEN AND STUDIES ON THE CELLULAR STRUCTURE OF THE CENTRAL NERVOUS SYSTEM

AVERAGE OXYGEN, PER CENT	MINIMAL OXYGEN, PER CENT	DURATION OF EXPERIMENT	HISTOLOGIC CHANGES				REMARKS
			CEREBRUM	CEREBELLUM	PONS	SPINAL CORD	
4.43	4.43	1½ hours	No	No	No	No	Died
4.54	4.36	3 days	-	-	-	-	Died
4.82	3.54	4 days	Yes +++	±	±	No	Extensive lesions
5.29	4.36	4 days	-	-	-	-	Died
4.86	4.58	5 days	Yes +++	No	±	No	Moderately extensive lesions
4.71	4.36	8 days	Yes +±	No	No	No	Few lesions

The type of changes observed in the large and small pyramidal cells of the cerebral cortex may be summarized as follows: (1) swelling; (2) pyknosis; (3) vacuolization; (4) degeneration (necrosis); and (5) satellitosis.

The cellular changes were essentially the same as those described after digitalis had been administered in toxic amounts. The lesions produced by digitalis were far more extensive and intensive than those produced by deprivation of oxygen. Fig. 5 illustrates the degenerative changes in the pyramidal cells after prolonged deprivation of oxygen.

D. Signs Observed in Animals While They Were Subjected to Systemic Deprivation of Oxygen.—An endeavor was made to keep the percentage of oxygen in the chamber at a level which produced only slight drowsiness in the animals. The cats seemed to breathe 4 to 5 per cent oxygen without much evidence of distress. When the percentage of oxygen fell too rapidly or was held at too low a level, the animals became restless and exhibited a panting type of respiration.

Sometimes cyanosis of the tip of the nose and tongue was observed. Vomiting occurred on two occasions. Ataxia was noted in several of

the animals when they were removed from the chamber for the daily feeding. This ataxia did not persist very long. Death occurred as the result of respiratory failure in three cats; electrocardiograms were taken on these three animals when death occurred—the respirations ceased before the heart stopped beating.

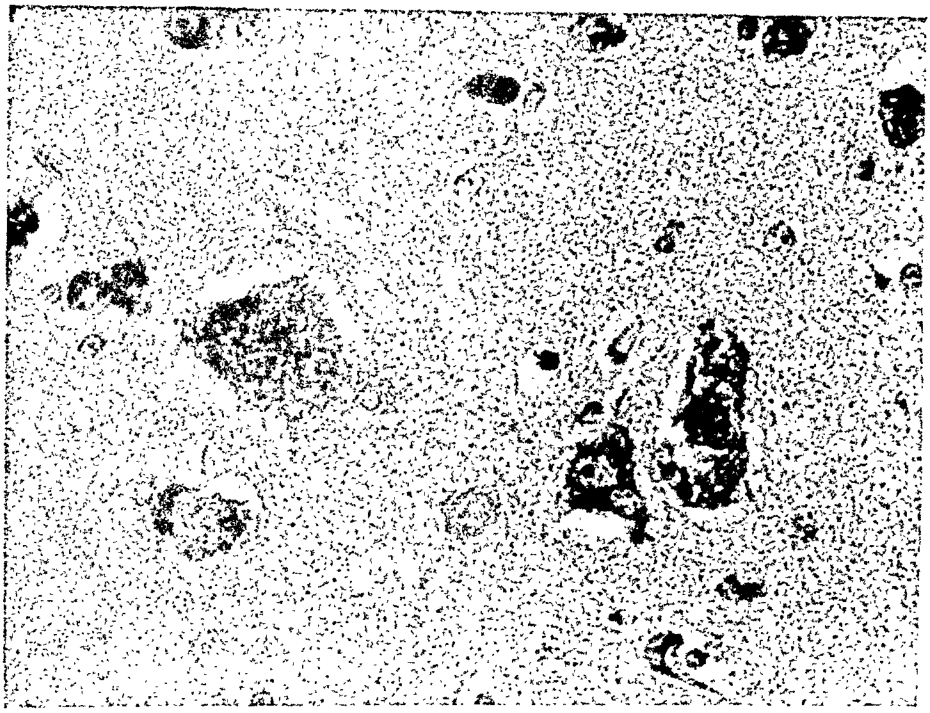

Fig. 5.—Degeneration of the pyramidal cells of the cerebral cortex after prolonged deprivation of oxygen (×450).

At any given low percentage of oxygen, the old animals showed more tendency to cyanosis and panting respiration than did the young animals. The old cats died sooner than the young ones while breating the same percentage of oxygen.

COMMENT

The experimental methods used in these studies were simple and readily controlled. The percentage of oxygen was checked by two independent methods. The necropsies were done immediately after the animals died or were killed. The myocardial and cerebral degenerative changes had to be definite before we counted them as myocardial or cerebral lesions. This avoided quibbling about borderline intracellular morphologic changes.

In order to avoid errors in the interpretation of these experimental results, it should be pointed out that these animals were subjected to rather severe grades of anoxia over long periods. We do not know how the cat and man compare in their relative sensitization to deprivation of oxygen. We wish to avoid giving the impression that, just because the electrocardiographic, myocardial, and cerebral changes after prolonged deprivation of oxygen resembled those seen after the admin-

istration of toxic doses of digitalis, the lesions produced by digitalis were the result of anoxia and nothing else. This conclusion is unwarranted. The fact that deprivation of oxygen may produce changes similar to those induced by toxic doses of digitalis may be interpreted as possible presumptive evidence, but certainly not as direct proof, that anoxemia may be one of the many factors involved in the production of myocardial and cerebral lesions by digitalis.

In order to avoid another error of interpretation, it may be worth while to emphasize that existing experiments of short duration (done by others) indicate that anoxia dilates the coronary arteries and increases the coronary blood flow.

SUMMARY

Histologic changes were observed in the myocardiums of animals which were subjected to prolonged systemic deprivation of oxygen over periods of three or more days. An endeavor was made to keep the concentration of oxygen near 4 to 5 per cent. One animal, which died one and a half hours after the inhalation of low percentages of oxygen, did not show any evidence of anatomic changes in the myocardium.

The myocardial lesions produced by deprivation of oxygen resembled those found in the heart after the administration of toxic doses of digitalis. They were focal in distribution and were most prominent in the papillary muscle and in the left ventricular wall.

The following is a summary of the prominent changes in the RS-T segment and the T wave after prolonged systemic deprivation of oxygen: (1) decrease or increase in the height of the T waves in one or more leads, (2) simple inversion of the T waves in one or more leads, (3) depression of the RS-T segment in one or more leads, (4) cove-plane, negative T_2 and T_3, and (5) negative T_1 and positive T_3.

The electrocardiographic changes, as a rule, disappeared when atmospheric air was introduced into the chamber.

Cellular changes were observed in the central nervous system after prolonged deprivation of oxygen. The changes were similar to those described by others after anoxia and to those observed after the administration of toxic doses of digitalis.

Old animals were more sensitive to deprivation of oxygen than young ones.

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Clinical Report

INTRAPERICARDIAL ANEURYSM CAUSED BY CONGENITAL SYPHILIS

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As pointed out by Moore,[1] "cardiovascular lesions happen so rarely in congenital lues that they can be discarded as practically non-existent." For this reason, we feel that it is worth while to present the clinical and post-mortem observations on an 18-year-old girl who showed clear-cut signs of aortic insufficiency of the Hodgson type and aneurysm of the ascending aorta caused by congenital syphilis.

CASE REPORT

History.—Both parents are alive. The mother has had repeatedly positive blood Wassermann and Kahn reactions, and has aortic insufficiency of the Hodgson type and marked dilatation of the ascending aorta. She has had ten pregnancies, of which the first four were successful, and the offspring are alive and healthy; the fifth was spontaneously interrupted by abortion after seven months; the sixth was successful, and this offspring is our patient; the seventh was interrupted by abortion after eight months; and from the other three pregnancies, which were successful, two children died in infancy and one is alive and in good health. We were not able to examine any other relative of our patient.

At the age of 3 years, our patient was ill with what was diagnosed as meningitis. However, from that time until the beginning of the illness described in this paper, she felt well. For two weeks before her admission to the hopital, she had nocturnal paroxysmal dyspnea on exertion, together with retrosternal pain and cough.

Physical examination.—Adenoidal facies and inadequate nutrition. Cardiovascular system: pulse regular, equal, and forcible. Blood pressure: 120/20. Forcible arterial pulsations in the neck. Apex beat in the sixth left intercostal space outside the mammillary line, with elevation of the thoracic wall. A marked thrill was felt in the second and third right intercostal spaces, where there was a double murmur (systolic and diastolic) which was transmitted to the rest of the precordial area; the systolic component was the more intense. The heart sounds were normal.

The rest of the physical examination was negative. The blood Wassermann and Kahn reactions were positive; the blood urea nitrogen and glucose were normal, as was the urine.

Roentgenologic examination showed a heart of mitral-aortic configuration, markedly enlarged (Fig. 1). The ascending aorta made a

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bulge to the right, and the auriculovascular point was lowered. The superior vena cava was distended. The pulsations of the left ventricle were of the excited type, and those of the ascending aorta were expansile. In the left oblique posterior view the considerable enlargement of the ascending aorta, with its expansile pulsation, and the enlargement of the left ventricle were verified. The lateral view showed marked enlargement of the anteroposterior diameter of the heart and disappearance of the retrosternal clear space as a result of the aortic enlargement. By means of a radiopaque meal, it was found that the entire esophagus was deflected backwards. There was a marked pulmonary design, and the right hilum was covered by the shadow of the ascending aorta.

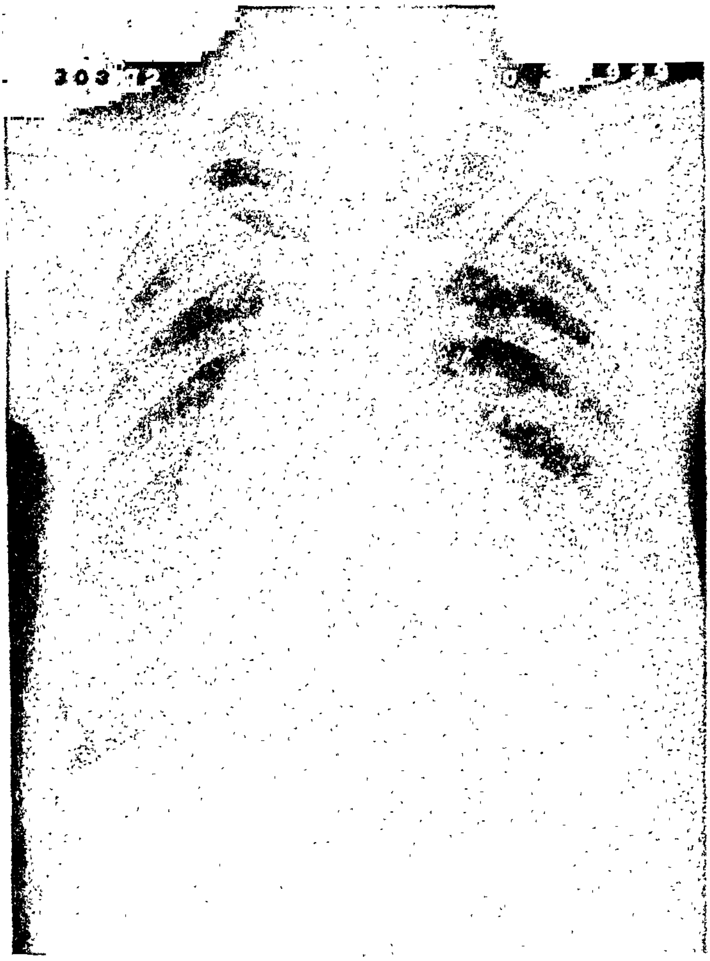

Fig. 1.

The electrocardiogram showed sinus tachycardia and bundle branch block of the common type.

Treatment, consisting of the administration of bismuth carbonate and cardiotonics, was begun. The patient improved only slightly, and, after two and one-half months, suffered again with nocturnal paroxysmal dyspnea and died during an attack of cardiac asthma.

Necropsy.—Macroscopically, it was found that the heart was enlarged, particularly the left ventricle, which showed evident hypertrophy and dilatation of both inflow and outflow paths (Fig. 2). There were marked retraction and hardening of the aortic sigmoid valves; and a fusiform

aneurysm of the whole ascending aorta, of a size somewhat greater than a hen's egg, was found (Fig. 2, *a*). The pericardium at that level was somewhat thickened.

Microscopic examination was performed by Dr. M. A. Etcheverry, who reported the following: The root of the aorta immediately above the region of the annulus (Fig. 3), and especially along the wall of the vessel upwards nearer the aneurysmal dilatation (Fig. 4), showed thinness and fibroid transformation of the intima, the limits of which with the media were not clear; the elastic tissue of the media was disorganized and dissociated by thin bundles of fibroid tissue in large zones; the adventitia was thickened and discretely sclerosed; its small blood vessels had a decreased diameter and thickened walls.

Fig. 2.

At the level of the aneurysmal dilatation (Fig. 5), the lesions were even more pronounced. The aortic wall was thinner, and all of its layers were affected. The intima was thinner, fibrous, and had deposits of hematic pigment. The limits with the media were confused. The latter was also thin, and its musculoelastic tissue was markedly dissociated and disorganized by thick bands of hyalinized fibrous tissue. This fibrous replacement was particularly marked in the external part of the media, where, sometimes, the border of the adventitia was barely indicated by a tenuous band of fibroelastic tissue; it was not of nodular character, but in the form of long longitudinal bands, more or less large in different places. The adventitia showed its greatest thickness in this area; in some parts it formed nearly half of the wall of the aorta. There was also sclerosis; large collagenous bundles, partially hyalinized, and arranged in an undulate form parallel to the axis of the vessel, were present, and a few fibrocyte nuclei were visible. No Aschoff's nodules were to be seen. The vessels of the adventitia were scarce; their walls were thick and fibrous, and their lumina were narrow or even obliterated. Around some of them a few leucocytes were seen, predominantly lymphocytes and plasmocytes. Nowhere did the sclerosis of the adventitia acquire a nodular aspect.

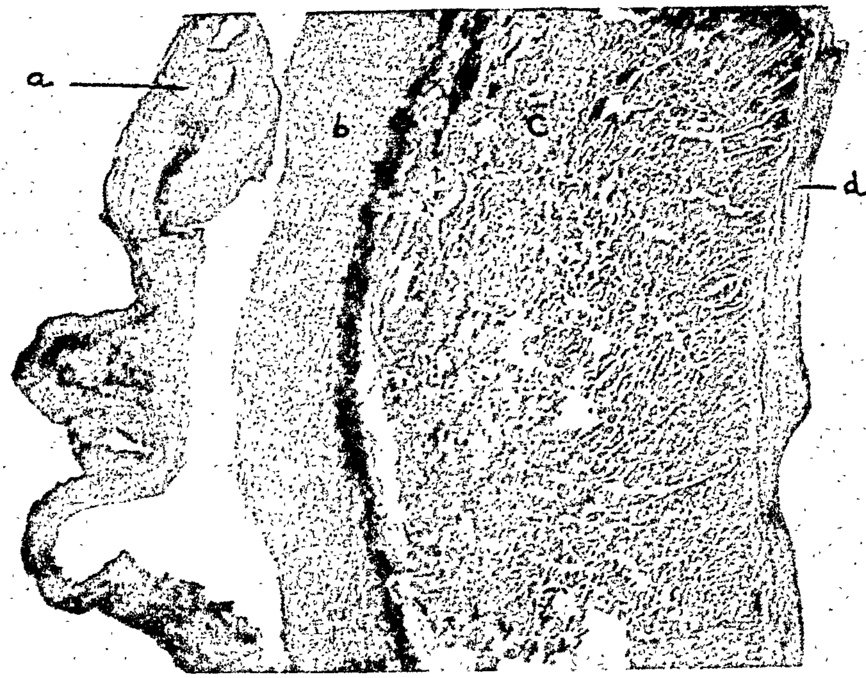

Fig. 3.—*a*. Aortic valve; *b*, aorta; *c*, myocardium; *d*, pericardium.

Fig. 4

Fig. 5.

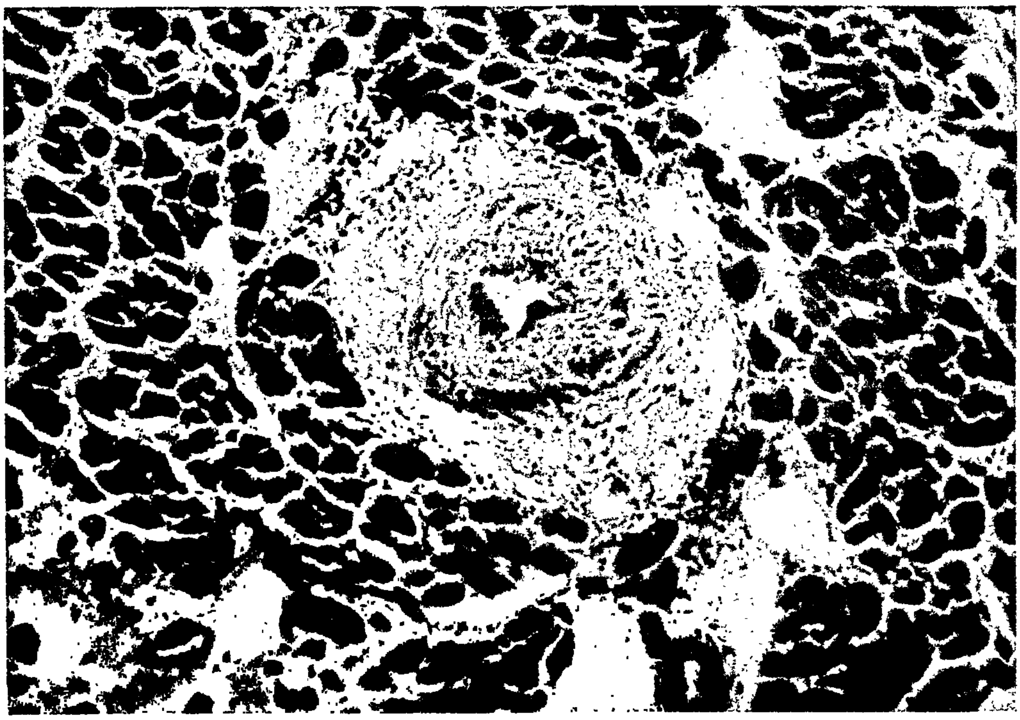

Fig. 6.

In the aortic arch there was an atheromatous plaque, partially calcified, and at its level the intima and adventitia were practically normal.

Argentic impregnation of sections of the aortic wall to demonstrate the Treponema gave negative results.

Fig. 3 shows one of the aortic valves in which chronic scleroretractile lesions were present.

In the posterior wall of the left ventricle, lesions were found that were interpreted as the result of an old, healed, myocardial infarct.

Some of the myocardial intramural vessels showed no lesions. Others, however, and particularly those in one of the sections of the papillary muscles of the left ventricle, showed lesions of chronic panvasculitis, affecting the intima, media, and adventitia. These were small vessels, with thickened walls and reduced lumina. A more detailed analysis revealed that, in some of them, there were disorganization of the endothelium, which appeared irregular and proliferated, proliferation and fibrous transformation of the intima, and thickening of the media and adventitia, with fibrosis of the latter. In others (Fig. 6), analysis revealed discrete lymphoplasmocyte and polynuclear infiltration of the adventitia, which had extended itself in the neighborhood between the myocardial fibers.

The endocardium showed slight thickening and subendocardial fibrosis.

The principal lesions in the sections which we have described may be summarized as follows:

Aorta.—Chronic endaortitis, scleroatrophic in parts, sclerohypertrophic in others. In the aortic arch, atherosclerotic lesions, partially calcified.

Chronic, destructive, scleroatrophic mesaortitis.

Marked sclerotic periaortitis, with residues of mononuclear infiltration.

Chronic, scleroretractile lesions of the sigmoid valves.

Endocardium.—Chronic fibrous endocarditis.

Myocardium.—Healed infarct in the wall of the left ventricle. Discrete, chronic, interstitial myocarditis in the remainder. Total absence of Aschoff's nodules or other specific lesions. Localized lesions of chronic panvasculitis of stenotic tendency.

DISCUSSION

Lesions of the aorta caused by congenital syphilis, especially aneurysmal dilatation, are very rare. Matusoff and White[2] stated that involvement of the heart and aorta in cases of congenital syphilis is rare; and Calvin and Nichamin[3] concluded that, although many authors believe that syphilis is the principal cause of aneurysms in children and adults, a careful study of the question does not confirm that assertion. On the other hand, Bronson and Sutherland[4] state that anatomic observations on congenitally syphilitic newborns suggest that many of the aneurysms of adolescents and young adults may be caused by congenital syphilis, and mention in this respect the observations made by Nixon[5] on a 20-year-old girl with an aneurysm of the abdominal aorta.

There has been very little mention in the literature of cases in which necropsy has been performed. Escudero[6] reported observations on two

congenitally syphilitic brothers, 4 and 6 years of age, who had a cylindrical dilatation of the aortic arch, together with aortic stenosis. Wilson and Marcy[7] appear to have been the first to verify by necropsy the existence of an aortic aneurysm caused by congenital syphilis. Navarro,[8] Acuña,[9] and Heiman[10] presented cases of aneurysm of the thoracic aorta in children, 12, 13, and 14 years of age, with congenital syphilis and positive blood Wassermann reactions. Similar observations were made by Herrera Vegas,[11] Paul,[12] and Schulte.[13] Acuña, Winocur, and Orosco,[14] at necropsy on a congenitally syphilitic girl, 6 years of age, verified the existence of multiple aneurysms of the aortic arch and thoracico-abdominal aorta, and mentioned the discovery by Muniagurria[15] of an aneurysm in a baby 8 days old. Recently, Neiman and Marks[16] presented a similar case, that of a girl 10 years of age upon whom a thorough anatomic study was made.

Our patient had all the symptoms of aortic insufficiency and an aneurysm of the ascending aorta, namely, a systolic thrill and double murmur, with maximum intensity in the second and third right intercostal spaces, dilatation of the ascending aorta, with localized expansile pulsations, etc., and this diagnosis was confirmed by necropsy.

The cause of the disease appears to us undoubtedly to have been syphilis; in fact, the Wassermann and Kahn reactions were positive, and no antecedent rheumatic fever or other infections were present. Furthermore, the microscopic study of the anatomic sections supported the clinical presumption; the lesions in the wall of the aorta were similar in every respect to those described by Neiman and Marks,[16] upon which they based their diagnosis of a syphilitic process.

Considering the absence of a history of syphilitic infection (the virginity of the patient supported this) and the evidence that the mother had syphilis (positive serologic reactions and the history of abortions), we feel that the congenital origin of the syphilitic infection cannot be doubted.

We wish to point out that the interval between the appearance of the first symptoms and the time of death was very short. This is in accordance with the observations of Cossio and Fustinoni,[17] who state that "the younger the patient, the more severe is the course of cardio-aortic syphilis when it takes the form of aortic insufficiency or aortic aneurysm."

SUMMARY

The authors comment upon observations made by clinical examination and further verified by necropsy in the case of an 18-year-old girl with intrapericardial aneurysm of the aorta caused by congenital syphilis. A review of similar cases from the literature is given. The rapid course of the malady is pointed out: only three months elapsed between the first symptoms and the time of death.

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Abstracts and Reviews

Selected Abstracts

Page, I. H.: The Occurrence of a Vasoconstrictor Substance in Blood During Shock Induced by Trauma, Hemorrhage and Burns. Am. J. Physiol. 139: 386, 1943.

Shock, whether elicited by tourniquets placed around the extremities, by stripping and exposing the intestines, or by hemorrhage and burns, is associated with the appearance in the plasma of a substance which causes vasoconstriction in rabbits' ears perfused with either calcium-free Ringer's solution or plasma. It does not originate in the kidneys or adrenal glands, nor does destruction of the spinal cord or renal denervation prevent its appearance. Evidence gathered from application of a method depending on "fatiguing" the vascular musculature suggests, if the validity of the method is acceptable, that the vasoconstrictor action of plasma from burned, bled, and shocked dogs is caused by identical or very similar substances. Furthermore, it differs from the vasoconstrictors present in hypertensive's (human and canine) plasma and in serum (human and canine). None of these vasoconstrictors seem to be histamine. This belief is confirmed by experiments on isolated intestine which show that serum causes marked contraction while plasma from burned or shocked dogs causes none.

AUTHOR.

Leeds, S. E.: The Effects of Occlusion of Experimental Chronic Patent Ductus Arteriosus on the Cardiac Output, Pulse and Blood Pressure of Dogs. Am. J. Physiol. 139: 451, 1943.

A condition similar to patent ductus botalli was produced in dogs by lateral anastomosis of the aorta to the left pulmonary artery and by end-to-side anastomosis of the left subclavian to the left pulmonary artery.

Studies were made of both the immediate and late effects of production of the experimental ductus arteriosus on the cardiac output, pulse, and content of oxygen in the blood.

A study was also made of the immediate effects of occlusion of chronic experimental ductus arteriosus on the pulse, systemic blood pressure and that of the pulmonary artery and the cardiac output.

In the experiments of long standing the flow of blood through the experimental ductus arteriosus was calculated.

The significance of the findings as related to surgical ligation of patent ductus botalli in human patients is suggested.

AUTHOR.

Bozler, E.: Tonus Changes in Cardiac Muscle and Their Significance for the Initiation of Impulses. Am. J. Physiol. 139: 477, 1943.

The after-potentials of cardiac muscle previously described are accompanied by changes in "tonus." In fresh muscle the tension drops slightly below the previous level corresponding to the positive after-potential observed under the same conditions. This phenomenon is significant because it indicates the presence of a

tonic contraction in "resting" muscle. After treatment with an excess of calcium ions the responses are followed by oscillatory changes in tension.

The tonus changes and the local potentials are probably manifestations of a more fundamental process, a fluctuation in resting metabolism. The mechanical changes are weak and hardly play any role as such. Their chief interest lies in their relation to the automaticity and rhythmicity of the muscle. It may be assumed that an increase in metabolism causes a rise in tonus and a decreased surface polarization. The decrease in polarization in turn may be considered as the last link in the chain of processes leading to the discharge of an impulse.

AUTHOR.

Rosenblueth, A., and Del Pozo, E. C.: The Changes of Impedance of the Turtle's Ventricular Muscle During Contraction. Am. J. Physiol. 139, 514, 1943.

The changes of electrical impedance during the activity of the turtle's ventricle were measured by means of an alternating current bridge and recorded from a cathode-ray oscillograph.

The impedance to alternating currents of 30 to 10,000 cycles per second and of 0.04 to 0.06 ma. increases during activity. The increase begins approximately at the same time as contraction, but it outlasts the mechanical events. There is no parallelism between the impedogram and the electrogram. Brief electrical and mechanical responses involve a brief impedance variation.

Upon repetitive stimulation a long enduring impedance change may ensue.

The early part of the ventricular electrogram is not attended by any striking change of impedance.

AUTHORS.

Kosupkin, J. M., and Olmsted, J. M. D.: Slowing of the Heart as a Conditioned Reflex in the Rabbit. Am. J. Physiol. 139: 550, 1943.

It is possible so to condition a rabbit as to slow its heart rate by using inhalation of ammonia as the unconditioned stimulus and the ringing of a bell as the conditioned stimulus.

AUTHORS.

Nahum, L. H., Hamilton, W. F., and Hoff, H. E.: The Injury Current in the Electrocardiogram. Am. J. Physiol. 139: 202, 1943.

Injury to the right ventricle causes an upward displacement of the diastolic base line in the three standard leads of the electrocardiogram. Injury to the left ventricle produces a downward displacement of the diastolic base line.

During systole there is a return of the string to the isopotential level which constitutes the S-T segment.

In reality, therefore, elevated S-T segments must be interpreted as due to an injury potential resulting from left ventricular damage, which produces in the electrocardiogram a downward displacement of the diastolic base line.

Depressed S-T segments must be interpreted as due to an injury potential resulting from right ventricular damage, which produces in the electrocardiogram an upward displacement of the diastolic base line.

AUTHORS.

Rosenblueth, A., Daughaday, W., and Bond, D. D.: The Electrogram of the Turtle's Heart. Am. J. Physiol. 139: 464, 1943.

Evidence is presented which indicates that the electric phenomena recorded from leads on an intact and an injured region of the turtle's ventricle are due to

changes which occur in the intact, not the injured part of the muscle. This record may be called monotopic, to avoid the use of other ambiguous terms. This electrogram exhibits several components which may vary independently. The significance of some of these components is discussed.

The records with leads from intact to intact tissue are influenced by the position of the leads with respect to the stimulated region. They may also be modified in the course of a series of responses. These records may be called ditopic, since they represent the algebraic summation of two monotopic records.

The electric and the mechanical phenomena of the ventricle are largely independent.

AUTHORS.

Garvin, C. F.: Gallop Rhythm—Incidence and the Influence of Age, Race, and Sex. Am. J. M. Sc. 205: 814, 1943.

Of 790 consecutive, adult, autopsied patients dead of heart disease, 199 (25.2 per cent) had had gallop rhythm due either to auricular contraction or a third heart sound. Gallop rhythm occurred most frequently in hypertensive heart disease and coronary artery disease; one out of every three patients had this type of rhythm. Cor pulmonale was associated with gallop rhythm in about one case in five. Only one of ten patients who died of rheumatic heart disease or syphilitic heart disease had gallop rhythm.

The average age of death of 93 patients with hypertensive heart disease and gallop rhythm was 49.5 years, of 171 patients with hypertensive heart disease and no gallop rhythm, 58.8 years. Patients with coronary artery disease and gallop rhythm (55) averaged 57.3 years at death; 122 patients with coronary heart disease and no gallop rhythm averaged 64.4 years. Both of these differences seem to be statistically highly significant. Even if patients with auricular fibrillation are excluded (such patients rarely have gallop rhythm and are apt to be older), it still appears that the average age at death of cardiac patients with gallop rhythm is less than the average age of cardiac patients without gallop rhythm.

When patients with hypertensive and/or coronary heart disease were grouped together, it was found that, of 326 white patients, 100 (30.7 per cent) had a gallop rhythm, while of the 115 colored patients, 48 (41.7 per cent) had a gallop rhythm. This seems to indicate that colored patients with fatal hypertensive heart disease and/or coronary heart disease, show a higher incidence of gallop rhythm than white patients. It is thought that this is really a manifestation of the influence of age, for the average age at death of the colored patients was less than that of the white patients.

No association between gallop rhythm and sex was demonstrable.

AUTHOR.

Mazer, M., and Reisinger, J. A.: Criteria for Differentiating Deep Q_3 Electrocardiograms From Normal and Cardiac Subjects. Am. J. M. Sc. 206: 48, 1943.

A series of 102 electrocardiograms with significantly deep Q_3 waves has been analyzed. Criteria have been suggested to aid in differentiating those from normal and diseased hearts.

AUTHORS.

Evans, W., and Hunter, A.: Chest Lead CR_7 in Cardiac Infarction. Brit. Heart J. 5: 73, 1943.

A new chest lead, CR_7 is described and has been tested in the differential diagnosis of cardiac infarction.

The lead proved to have a limited value in identifying posterior infarction, but it was superior to the limb leads. The authors' experience has emphasized the importance of T_2 in posterior infarction, for in 30 out of 32 patients it supplied the evidence necessary for the diagnosis. In contrast, T_2 in anterior infarction was less reliable, and T in CR_7 was often its superior, although inferior to T in R_4.

CR_7 had greatest value in distinguishing between the T_2 and T_3 inversion of posterior infarction and similar changes found in heart failure from emphysema, in pericardial disease, in congenital heart disease, and occasionally in healthy subjects. This new chest lead also helped in the diagnosis of hypertension and aortic valvular disease when complicated by anterior cardiac infarction.

AUTHORS.

Sharpey-Schafer, E. P.: Potassium Effects on the Electrocardiogram of Thyroid Deficiency. Brit. Heart J. 5: 85, 1943.

The flat T wave of thyroid deficiency became upright after potassium. Inverted T waves also became upright, a response which is similar to that in preponderance of a ventricle and unlike that of myocardial infarction. A case of Addison's anemia showed accentuation of S-T depression.

AUTHOR.

Sharpey-Schafer, E. P.: Potassium Effects on T-wave Inversion in Myocardial Infarction and Preponderance of a Ventricle. Brit. M. J. 5: 80, 1943.

T-wave inversion due to myocardial infarction is further inverted by raising the serum potassium, while T-wave inversion due to preponderance of a ventricle becomes upright after potassium.

The method is useful in analysis of difficult electrocardiograms. It is suggested that T inversion in ventricular preponderance is an S-T change, not a T-wave change.

AUTHOR.

Shapiro, M. J., and Keys, A.: The Prognosis of Untreated Patent Ductus Arteriosus and the Results of Surgical Intervention: A Clinical Series of 50 Cases and an Analysis of 139 Operations. Am. J. M. Sc. 206: 174, 1943.

Diagnosis of patent ductus arteriosus can be made with great certainty, and complications making surgical ligation unadvisable are readily recognized.

The great majority of patients with this defect suffer no serious disability or restriction of activity during most of their lives, but their life expectation is greatly shortened by the continued presence of the defect.

Experience to date shows that ligation of the uninfected ductus can be made with a mortality of less than 10 per cent.

Ligation of the ductus in the presence of subacute bacterial endarteritis offers an even chance of survival in the face of practically certain death without ligation.

The danger of development of subacute bacterial endarteritis after successful ligation cannot properly be estimated as yet.

Six case histories are cited which illustrate opposing arguments for and against ligation.

An analysis is presented of the results of 140 operations to ligate the ductus.

It is concluded that the majority of patients with patency of the ductus arteriosus should be sent to surgery for ligation after careful clinical studies have been made on them.

Ligation should be attempted immediately if subacute bacterial endarteritis develops.

Ten patients with uninfected patent ductus arteriosus have been operated upon by Dr. O. N. Wangensteen at the University of Minnesota Hospital, the last eight cases with complete success. As far as is known, in none of them has there been a recurrence of signs indicating recanalization.

AUTHORS.

Bain, C. W. C., and Parkinson, J.: Common Aorto-Pulmonary Trunk: A Rare Congenital Defect. Brit. Heart J. 5: 97, 1943.

A common aorto-pulmonary trunk, as an isolated gross congenital malformation, was found at death in a man of 18 years, who had always been cyanosed and breathless. Electrocardiograms, radiographs, and pathologic details are recorded. The *malformation cannot be classified as persistent truncus arteriosus*, because there was neither a defect of the interventricular septum, nor any abnormality of the aortic and pulmonary valves.

AUTHORS.

Baker, L. A., Sprague, H. B., and White, P. D.: The Clinical Significance of Loud Aortic and Apical Systolic Heart Murmurs With Diastolic Murmurs. Am. J. M. Sc. 206: 31, 1943.

Determination of the status of 187 private patients who showed loud systolic murmurs, best heard at either the apex or aortic area, but no diastolic murmurs, ten to twenty-one years after they were first examined, resulting in finding that 155 (82.5 per cent) were dead. Death was due to heart disease in 122 (78.7 per cent).

Seventy-four (47.7 per cent) of all deaths occurred within a year after the first examination, while 110 (70.8 per cent) of the deaths occurred within three years.

The outlook for the younger patients with rheumatic heart disease was somewhat better than for those with heart disease of ''degenerative'' or uncertain etiology. In spite of the high death rate, only 24 of the 155 deaths occurred under the age of 50 years. The death rate was lower among females for the ten-year period but equaled that of the males by the end of fifteen years. Of the deaths among those with rheumatic heart disease, 24 per cent were due to subacute bacterial endocarditis. Those with larger hearts had a higher mortality. Despite these prognostic trends, however, it is impossible to predict with any high degree of assurance the course of any particular case.

An interesting and important observation is that some cases, originally diagnosed as having mitral regurgitation because of a loud apical systolic murmur, were later found to have aortic stenosis, which, in the course of ten to fifteen years, tended to precipitate abrupt left ventricular failure (acute pulmonary edema). The clue to these cases lies in the fact that the loud, somewhat harsh, systolic murmur heard at the apex is also heard at the aortic valve area, although perhaps less loudly. The murmur is primarily an aortic systolic murmur transmitted to the apex as well as into the neck vessels; a mitral regurgitant murmur is often heard at the lung bases (and in the left axilla) but not at the aortic valve area.

It is evident that loud systolic murmurs at the cardiac apex or aortic valve area are clinically important even in the absence of diastolic murmurs and a well-marked cardiac enlargement.

AUTHORS.

Bloom, F.: Structure and Histogenesis of Tumors of the Aortic Bodies in Dogs. Arch. Path. 36: 1, 1943.

Two similar tumors occurring spontaneously in the region at the base of the heart in dogs are reported. They had essentially the same anatomic location and histologic characteristics as the aortic bodies. It is considered, therefore, from the morphologic evidence, that the tumors originated from these structures. The aortic bodies are homologous with the carotid body, and the specific cells are neuroepithelial sensory cells that function as chemoreceptors. In view of the complex nature of the chemoreceptors, it is suggested that neoplasms of these structures be designated as tumors of the aortic bodies and tumors of the carotid body.

AUTHOR.

Peel, A. A. F.: Anginal Pain in Myxedema. Brit. Heart J. 5: 89, 1943.

Several types of anginal pain may occur in myxedema.

Angina of effort occurs frequently when there is independent heart disease and occasionally with an uncomplicated myxedema heart. In the presence of independent heart disease, angina is sometimes aggravated, sometimes alleviated, and sometimes unaffected by thyroid therapy. For many patients there is an optimum dose, up to which improvement results, but beyond which pain is aggravated; the optimum dose is often sufficient to procure great improvement in the patient's general condition and to permit a fair amount of activity; in favorable cases the angina is abolished on the optimum dosage. When a patient with myxedema and independent heart disease suddenly develops effort angina during thyroid treatment and apart from an increase in dosage, the cause is frequently a small coronary occlusion; caution suggests that the dose should be temporarily reduced or discontinued; but once the stage of convalescence has been reached, resumption of therapy does not aggravate the pain, and there seems to be no reason for withholding the benefits of the drug.

A constant pain or ache, aggravated during effort, and tending to be associated with attacks of collapse, occurs in some cases of mild or subclinical myxedema; it is referred to as the "abortive myxedema heart of Zondek." It improves with thyroid therapy, but in these cases, too, there may be an optimum dose. If unrecognized and untreated, the patients may develop a clinical myxedema or a typical angina of effort.

Spasmodic angina occurred in two cases. Both may have had very early hypertension, but neither had any obvious or advanced complicating heart disease. In one, the possibility of hypoglycemia was considered; the attacks ceased on treatment with thyroid and a dose of glucose at bedtime. In the other, there was a complicating anemia; the attacks ceased when this was treated and before any thyroid was given. In neither case did thyroid aggravate the spasmodic angina nor did it produce an effort angina.

The occurrence of anginal pain in a myxedematous patient does not contraindicate the cautious use of thyroid; only when pain develops in response to an increased dosage is there justification for blaming the drug, and even then it may be tolerated at a later date.

AUTHOR.

Lange, K.: A Recording Sphygmotonograph: A Machine for the Continuous Recording of Systolic and Diastolic Arterial Pressure in Man. Ann. Int. Med 18: 367, 1943.

A machine is described which automatically takes continuous records of the systolic as well as diastolic blood pressure of man.

The principle and the detailed construction are shown and the mechanical arrangements and working conditions discussed. The inertia of the machine is shown and the meaning of the obtained tracings are discussed.

A simple mechanical contact device is not satisfactory for registering the diastolic pressure since it is dependent on the magnitude of the oscillations instead of on the steepness of the ascending branch. A heated wire system (balometer) is used to transform the puffs of air into electric currents.

The steepness of the ascending branch of the diastolic oscillation is an exact criterion for the diastolic pressure.

The accuracy of the sphygmotonograph was proved by comparisons with the auscultatory method in 109 patients. The average difference for the systolic pressure was 0.06 mm. Hg, for the diastolic pressure 4.0 mm. Hg.

Records taken from both arms of the same patient with two machines are identical.

Taking uninterrupted records for a period of thirty minutes, with partial arrest of the circulation in the limb concerned, does not produce any detrimental effect on the vessels, nerves, or muscles.

The partial arrest of circulation and the pressure on the limb does not produce changes in the blood pressure.

Comparative measurements with the Korotkov method, using a recording microphone instead of the stethoscope, show the accuracy of the syphgmotonograph.

Many normal persons show Mayer-Traube-Hering waves of a wave length of about 30 seconds and a height up to 12 mm. Hg in size, under excitement and impaired breathing conditions.

Even slight mental work or excitement may cause a considerable increase in diastolic and systolic blood pressure, especially in individuals in the very beginning of hypertension.

AUTHOR.

Fishback, H. R., Dutra, F. E., and MacCamy, E. T.: The Production of Chronic Hypertension in Dogs by Progressive Ligation of Arteries Supplying the Head. J. Lab. & Clin. Med. 28: 1187, 1943.

Chronic hypertension has been produced in dogs by ligation, in series, of the arteries supplying the head.

Removal or manipulation in situ of the carotid sinuses alone has no prolonged effect on the blood pressure of dogs.

AUTHORS.

Warthin, T. A., and Thomas, C. B.: Studies in Experimental Hypertension. I. Phenol Red Excretion and Renal Blood Flow in Hypertension of Renal Origin. Bull. Johns Hopkins Hosp. 72: 203, 1943.

Arterial hypertension was induced in five dogs with single explanted kidneys by partial occlusion of the renal artery. Two dogs died in uremia, one and six weeks, respectively, after application of the clamps. Three dogs survived and were killed, three, seven, and eleven months, respectively, after the clamps were applied.

Studies of the rate of urinary excretion of phenol red, and of the renal blood flow through the extraction of phenol red by the kidney, were made in these animals before and after the renal arteries were constricted.

Immediately before or coincident with the onset of hypertension, a reduction in renal blood flow and phenol red excretion occurred. After three to four weeks, the renal blood flow returned to the control levels, but the hypertension persisted. In four to seven weeks, the phenol red excretion likewise returned to normal values.

These experiments indicate that chronic experimental hypertension of renal origin may persist after the renal blood flow has returned to normal.

Pentobarbital anesthesia in these animals produced a fall in blood pressure and renal blood flow both before and after hypertension was induced.

AUTHORS.

Alpert, L. K., and Thomas, C. B.: Studies in Experimental Hypertension. II. The Effect of Dietary Protein on the Urea Clearance and Arterial Blood Pressure in Chronic Hypertension. Bull. Johns Hopkins Hosp. 72: 274, 1943.

Determinations of the clearance of urea during periods of varying protein intake were made in five dogs. Two of the dogs had chronic experimental hypertension of renal origin, two had chronic neurogenic hypertension, and one had normal blood pressure.

The urea clearance values were normal in all of the animals during periods of low protein intake and showed pronounced elevations when the dogs were fed diets high in protein.

Since variations in urea clearance are associated with parallel changes in renal blood flow, these results suggest that there may be no impairment of renal blood flow in dogs with chronic experimental hypertension.

The variations in arterial pressure during the experimental diets were not great and could not be correlated with the changes in protein intake or urea clearance.

AUTHORS

Alpert, L. K., and Lilienthal, J. L., Jr.: Studies in Experimental Hypertension. III. The Effect of Dietary Protein on the Clearances of Diodrast and Insulin by the Kidney in Chronic Hypertension. Bull. Johns Hopkins Hosp. 72: 286, 1943.

Simultaneous determinations of the renal clearances of diodrast, inulin, and urea were made in six dogs during periods of low and high protein intake. Two of the dogs had chronic hypertension of renal origin, had two chronic neurogenic hypertension, and two had normal blood pressures.

The clearance values of all the substances under consideration were much greater during the periods of high protein intake than during the low ones. The inulin and urea clearances were increased to a relatively greater degree than were the diodrast clearances.

No qualitative differences were noted in the response of the normal renal hypertensive and neurogenic hypertensive dogs to the changes in diet.

No significant anatomical abnormalities were found in the blood vessels, kidneys, or other organs of the dogs at post-mortem examination.

It is concluded that the blood flow and functional activities of the kidneys of dogs with chronic experimental hypertension may be unimpaired, and may react to the stimulus of increased dietary protein in a manner which is indistinguishable from the normal.

AUTHORS.

Talbott, J. H., Castleman, B., Smithwick, R. H., Melville, R. S., and Pecora, L. J.: Renal Biopsy Studies Correlated With Renal Clearance Observations in Hypertensive Patients Treated by Radical Sympathectomy. J. Clin. Investigation 72: 387, 1943.

Renal clearance studies performed on twenty patients with essential hypertension showed a significant correlation with the microscopic appearance of their respective renal tissues which were removed for biopsy at the time of sympathec-

tomy, i.e., the more severe the renal vascular disease, the more reduced were the glomerular filtration rate and the renal blood flow. In the cases with Grade 0 and I renal vascular disease, the renal clearance observations were either normal or only very slightly reduced. Only in Grade IV renal vascular disease was renal blood flow seriously reduced.

The filtration fraction was normal in seven out of eight cases in biopsy groups 0, I, and II. It was increased in six of eleven cases in biopsy groups III and IV. These findings indicate that constriction of the efferent glomerular arterioles was not present in the early stages of renal vascular disease.

Bilateral radical lumbodorsal splanchnicectomy had relatively little effect on renal clearance, when measured in the horizontal position. Although glomerular filtration was reduced in the immediate postoperative peroid about 20 per cent, within a year it returned to and continued to maintain its preoperative level. Renal plasma flow was essentially unchanged.

AUTHORS.

Corcoran, A. C., and Page, I. H.: Effects of Hypotension Due to Hemorrhage and of Blood Transfusion on Renal Function in Dogs. J. Exper. Med. 78: 205, 1943.

Renal blood flow is decreased by hypotension due to bleeding, and glomerular filtration rate is disproportionately decreased. After a first forty-minute stage of hypotension at about 60 mm. Hg, infusion of blood with consequent restoration of the general blood volume and arterial pressure usually results in a return to normal of renal blood flow and function although renal blood flow subsequently tends to decrease. The restoration of renal blood flow and function is associated with an increase of urine flow above the control level.

Diodrast clearance loses its value as a measure of renal plasma flow (a) during severe or prolonged hypotension, and (b) immediately after restoration of arterial pressure by infusion after a first stage of hypotension. In the former case (a), it is decreased in consequence of decreased renal extraction of diodrast flow through nephrons whose vascular resistance is low; (b) the disparity after transfusion is due to excretion of diodrast accumulated in the kidney tubules and, presumably, in the interstitial fluid during hypotension. The presence of diodrast and inulin in the renal interstitial fluid explains the addition of these substances to renal venous blood observed in some of these experiments. The shifting equilibrium of diodrast between renal plasma and interstitial fluid may explain some of the instances of low diodrast extraction observed in these experiments during transfusion after hypotension, and may explain also the incomplete renal extraction of diodrast under normal conditions.

Dogs with denervated kidneys respond to blood transfusion and restoration of arterial pressure by a disproportionately slow and incomplete return towards normal of renal clearance and, presumably, of renal blood flow. On the basis of these facts, it is suggested that high spinal anesthesia may interfere with recovery of renal circulation in cases of shock treated by transfusion.

Profound or prolonged and repeated hypotension due to bleeding decreases the ability of normal and denervated kidneys of intact and anesthetized dogs to respond to transfusion and the restoration of arterial pressure by proportionately increased clearance and plasma flow, apparently because of renal vasoconstriction due to the release of humorally circulating vasoconstrictor substances.

AUTHORS.

Jahsman, W. E., Durham, R. H., and Dallis, N. P.: Recognition of Incipient Thromboangiitis Obliterans in Young Draftees. Ann. Int. Med. 18: 164, 1943.

Thromboangiitis obliterans occurs in young draftees and should not be overlooked because of possible long-continued disability compensation if such draftees are accepted for active service.

Incipient stages of the disease may be recognized from the nail fold capillary picture described, together with a modification of the Gibbon and Landis dermatherm study.

In these early stages there is diminution in vasodilatation of mild to moderate degree in at least one lower extremity. In the four cases reported, the maximum temperature rise in the most involved extremity, after immersion of a forearm in water at 110° to 114° F., was from 2.5° to 4.8° C. below the accepted normal of 32° to 33° C. Later, with more actual occlusion, there is constant coldness of the skin as in arteriosclerosis obliterans and little or no temperature rise on exposure to heat.

Two of the patients did not show as low a level of skin temperature as is usually seen after exposure of the feet and legs in a cool room for thirty minutes. It might be speculated that with a more active inflammatory process in the vessels in this stage of the disease there might be less vasoconstricting ability. A more likely explanation is the individual differences that are bound to be found in the way of sensitiveness to cold, even with an early disease process present.

Having diagnosed the disease early, it should be possible to keep these young men reasonably free from symptoms and prevent complications by teaching them more moderate habits of living and meticulous care of the feet.

AUTHORS.

Blakemore, A. H., and Lord, J. W., Jr.: Restoration of Blood Flow in Damaged Arteries: Further Studies on a Nonsuture Method of Blood Vessel Anastomosis. Ann. Surg. 117: 481, 1943.

The problem of blood vessel anastomosis deserves important consideration in this war because advances in the control of serious infection and the possible use of anticoagulants afford, for the first time in the history of wars, a basis for success; the outstanding cause of the loss of limbs in this war will be damage to the blood supply.

Vitallium is presented as a nonirritating alloy suitable as a prosthesis for a vein graft bridging an artery or vein defect in a nonsuture method of vessel anastomosis using a single or double tube technique.

Carefully controlled experiments on dogs are presented, demonstrating that sulfathiazole by mouth contributed greatly to the success of delayed anastomoses of severed vessels in contaminated wounds. Using sulfanilamide in alternate wounds in a series of 77 anastomoses, it was noted to be of moderate but definite value.

The nonsuture method was shown to be highly successful in anastomosing the small femoral arteries of dogs, even in contaminated wounds twenty-four hours after section of the artery, and without the use of anticoagulants.

It is assumed that vein graft anastomoses of the severed primary artery in the war-wounded will prevent the loss of the extremity by gangrene if the anastomosis remained patent beyond the posttraumatic edema, up to fourteen days.

Experiments are presented showing that veins taken from one dog may continue to function in another when used as transplants to bridge vessel defects; for example, the successful reimplantation of limbs twenty-four hours after their removal. These experiments afford a prospect for the use of preserved veins as grafts for bridging vessel defects in the war-wounded as an alternate to the use of homoplastic transplants.

AUTHORS.

Bremer, J. L.: Congenital Aneurysms of the Cerebral Arteries: An Embryologic Study. Arch. Path. 35: 819, 1943.

The cerebral arteries are evolved from a capillary plexus arising from the earliest branch of the primitive aortic arch, which runs along the under side of the brain. From the rostral end of the plexus, branches go in front of the bulging

hemisphere and over its lateral surface, becoming the anterior and middle cerebral arteries. Another part of the plexus becomes the posterior cerebral artery, covering the diencephalon and midbrain. The anterior artery gains the mesial surface of the frontal lobe; the posterior supplies the similar surface of the posterior lobes that their expansion covers in the diencephalon. All cerebral arteries approach from the lesser curvature of the expanding hemisphere, and the interstitial growth of the latter during fetal life rapidly spreads the forks of their branches. Other growth changes have the same action. If these forks lack the media, the rapid spread may produce local aneurysms.

From all the cerebral arteries and from the main basal trunk, smaller branches dip into the brain substance and also supply the meninges. These also form plexuses. Proximal members of such plexuses may enlarge while their distal continuations degenerate and may thus become aneurysmal pouches from the main vessels. Both types may be true congenital aneurysms.

AUTHOR.

Rottino, A., and Poppiti, R.: Intimal Changes in Medial Degeneration of the Aorta. Arch. Path. 36: 201, 1943.

A report of a case of severe medial degeneration of the aorta with a tree bark type of intima is presented. Syphilitic mesaortitis and endoarteritis obliterans of the vasa vasorum were not present. It is contended that the intimal lesion in this case is not syphilitic and is secondary to mural weakness resulting from medial degeneration.

Brief mention is made of the incidence of intimal lesions in cases of medial degeneration.

AUTHORS.

Blalock, A.: Effects of Lowering Temperature of an Injured Extremity to Which a Tourniquet Has Been Applied. Arch. Surg. 46: 167, 1943.

The results of the experiments reported indicate that the use of a tourniquet on an injured extremity should be avoided whenever possible, but that, if some form of constriction is necessary, the temperature of the distal ischemic and anemic part should, if possible, be lowered by artificial means.

AUTHOR.

Essex, H. E., Herrick, J. F., Baldes, E. J., and Mann, F. C.: Observations on the Circulation in the Hind Limbs of a Dog Ten Years Following Left Lumbar Sympathetic Ganglionectomy. Am. J. Physiol. 139: 351, 1943.

Observations have been made on the blood flow in the femoral arteries of a dog at intervals over a period of ten years and two months. Blood flow was measured in both femoral arteries simultaneously under infiltration anesthesia before sympathetic ganglionectomy, and fifteen days, ten months twenty-five days, nine years two months, and ten years two months, after sympathectomy. Whereas the flow was twice as great in the left or sympathectomized limb as it was in the right or control limb fifteen days, and also ten months and twenty-five days after sympathectomy, the flow was almost the same in the two limbs nine, and also ten years after sympathectomy.

That the vessels of the sympathectomized leg were profoundly hypersensitive to epinephrine more than nine and ten years after sympathectomy was shown by a small injection of epinephrine, which caused such a marked constriction of the vessels of the sympathectomized side that the flow was zero for at least two minutes. The flow on the control side taken at the same time was only slightly altered.

Simultaneous plethysmographic records of the two hind feet further confirmed the observations on blood flow, since there was a transient decrease of the volume of the innervated foot but a very prolonged decrease of that of the denervated foot in response to small doses of epinephrine.

Histologic examination of a toe from each hind foot showed that the arterioles of the left or sympathectomized foot had undergone hypertrophy which was confined to the muscularis coat of the vessels. The vessels of the control side did not show hypertrophy.

AUTHORS.

Meneely, G. R., and Kaltreider, N. L.: A Study of the Volume of the Blood in Congestive Heart Failure. Relation to Other Measurements in Fifteen Patients. J. Clin. Investigation 22: 521, 1943.

In fifteen patients with severe congestive heart failure, the blood volume, arterial and venous blood pressure, arm-to-tongue circulation time, vital capacity, arterial and venous oxygen and carbon dioxide content and oxygen combining power, volume of packed red cells, plasma carbon dioxide combining power, and plasma total proteins were measured and are reported.

The blood volume was increased in all cases, and, in most, the increase was substantial.

There was great variability in the increase and in the degree to which the plasma and the cells contributed to the increase, and no statistically significant difference was observed between the increase in cell and plasma volume.

There was no simple correlation between the total blood volume and the other measurements made, nor between the venous pressure and the circulation time.

A negative correlation of moderate significance was found between the venous pressure and the plasma volume.

The logarithm of the circulation time bore a linear relation to the ratio between the transverse diameter of the heart and the internal diameter of the chest in eight cases where roentgenograms of the chest were taken.

The venous hematocrit and hemoglobin gave little indication of the actual volume of circulating cells.

There was a highly significant correlation between the degree of anoxemia measured by Lundsgaard's "capillary unsaturation" and the increase in cell volume.

In three patients who improved, all measurements tended toward normal, the plasma volume decreasing more than the cell volume. In the patients who grew worse, the reverse was the case.

AUTHORS.

Shipley, R. E., Gregg, D. E., and Schroeder, E. F.: An Experimental Study of Flow Patterns in Various Peripheral Arteries. Am. J. Physiol. 138: 718, 1943.

Flow patterns (and simultaneous intra-arterial pressure curves) have been optically recorded with an improved orifice-type flow meter in the renal, hepatic, superior mesenteric, femoral, axillary and common carotid arteries of dogs to which have been administered only anesthetic and anticoagulant.

A flow pattern may be characteristically distinctive of a given artery and its bed, but flow patterns in heteronymous arteries are found to exhibit wide variations in magnitude, timing, direction, and rate of flow, and in similarity of contour to their respective pressure pulses. Back flow components have been consistently found to exist in the femoral and axillary arterial flow patterns, frequently found in the common carotid patterns, while the renal, hepatic, and superior mesenteric have exhibited only forward flow.

A study has been made revealing the probable determinants of, and their interrelated influences upon, the phasic rate of inflow to a bed (flow pattern) under the above and other physiologic conditions.

Although the above analysis does not lend itself to a quantitative evaluation of the static and dynamic factors which initiate and moderate the phasic rate of inflow to a bed, it constitutes a basis for a qualitative evaluation of differences among, and changes in, flow patterns, recorded in the same or different arteries under various physiologic conditions.

AUTHORS.

Pritchard, W. H., Gregg, D. E., Shipley, R. E., and Weisberger, A. S.: A Study of Flow and Pattern Responses in Peripheral Arteries to the Injection of Vasomotor Drugs. Am. J. Physiol. 138: 731, 1943.

Optically recorded flow patterns (with an improved orifice type meter) together with the coexisting pressure pulses in the superior mesenteric, hepatic, renal, common carotid, axillary, and femoral arteries of anesthetized dogs are presented. The effects of intra-arterial and intravenous administration of vasodilator and constrictor drugs on the flow and pressure curves are shown. Following the system of analysis previously described, several series of curves have been examined with reference to changes in mean flow; relationship of mean flow to mean pressure; similarity of contour between patterns and pressure pulses; volume of pulsatile deviation from the mean rate of flow (dynamic volume-elastic properties of the vascular tree), and the vasomotor state of the bed (dilatation or constriction).

The generally accepted vasomotor responses to so-called dilator and constrictor drugs given intra-arterially were observed. However, in some records, and especially in those obtained following intravenous drug administration, changes in the vasomotor state of the bed could not be determined because of the overlapping of central and peripheral drug effects.

The dynamic volume-elastic component is reduced, except in the common carotid artery, by vasoconstrictor drugs given intra-arterially, while vasodilators usually increase this fraction during most of the period of drug action.

The injection of constrictor drugs, either intravenously or intra-arterially, may cause the appearance or augmentation of back flow in the patterns of all peripheral arteries so far studied. Dilators may introduce backflow in the common carotid pattern and greatly augment that pre-existing in the common carotid, axillary, and femoral patterns.

The interrelationship of the determinants associated with vasomotor drug effects is considered and discussed.

AUTHORS.

Hiatt, E. P., and Garrey, W. E.: Drug Actions of the Spontaneously Beating Turtle Ventricle Indicating Lack of Innervation. Am. J. Physiol. 138: 758, 1943.

Isolated strips of the ventricle of the turtle heart will beat spontaneously and regularly if bathed in a well-oxygenated physiologic saline solution containing potassium and calcium in equivalent molar concentration but having less potassium than turtle serum.

These ventricular strips do not show inhibition either of impulse initiation or contractility when treated with acetylcholine (plus eserine) or pilocarpine in concentration far in excess of those required to inhibit the auricle and the frog ventricle. This confirms previous work indicating that the turtle ventricle lacks a vagus nerve supply.

Adrenalin and ephedrine cause a small increase in the amplitude of the contractions of ventricular strips but the effect is quite small compared with the effect on the auricle and on the frog ventricle. It is suggested that this indicates a lack of sympathetic nerve supply.

A small excess of potassium, which has little effect on the auricle or the frog ventricle, causes cessation of the beat of fresh turtle ventricle strips. The effect is not on the contractile process. The sensitivity of these strips of turtle ventricle to potassium decreases with time after excision.

Calcium excess causes an increase in the amplitude of both auricular and ventricular contractions.

It is indicated that acetylcholine, pilocarpine, adrenalin, and ephedrine have their principal effects on the heart muscle only through the receptor substance which accompanies innervation. Adrenalin and ephedrine have a slight stimulating action on the aneuric myocardial tissue. Potassium and calcium appear to have a definite action directly on the myocardial cells lacking the receptor substance.

AUTHORS.

Leathem, J. H., and Drill, V. A.: The Effect of Diethylstilbestrol on the Blood Pressure of Normal and Hypophysectomized Rats. Am. J. Physiol. 139: 17, 1943.

The daily injection of stilbestrol into normal rats produces a gradual rise in systolic blood pressure, reaching hypertensive levels in many cases.

The systolic blood pressure of the untreated hypophysectomized rat decreased, on the average, 30 to 35 mm. below normal within ten days after hypophysectomy. Rats hypophysectomized for seven months had a blood pressure stabilized at this low level.

The injection of hypophysectomized rats with stilbestrol produced a fall in blood pressure below that of operated controls.

AUTHORS.

Book Review

IRRIGACION NORMAL DEL NODULO DE KEITH Y FLACK, TAWARA, HAZ DE HIS Y SUS RAMAS: By Dr. Eduardo F. Lascano, El Ateneo, Buenos Aires, 1942, 97 pages, 25 illustrations.

This monograph deals with the normal blood supply of the S-A node, the A-V node, and the His bundle and its branches. The coronary vessels were injected with gelatin, paraffin, or celloidin, with the addition of dyes or radiopaque substances. Dissection, roentgenograms, corrosion, and diaphanization were used.

The S-A node receives its blood supply from one auricular artery only. This may be one of the anterior, lateral, or posterior auricular ascending branches of the right and left circumflex arteries. There are, therefore, six different possibilities. This artery is larger than the others, and gives origin to a pericaval ring. The artery of the S-A node starts from this ring and runs along the sulcus terminalis.

The main artery of both the A-V node and the His bundle is the first posterior perforating artery, or the ramus septi fibrosi of Haas. It anastomoses with other vessels.

The right branch of the His bundle receives blood from three different groups of vessels:

1. An anastomotic plexus supplied by the ramus septi fibrosi, the ramus septi ventriculorum superior, the ramus cristae supraventricularis, and the first anterior perforating arteries.

2. A second plexus supplied by the ramus limbi dextri, the plexus of 1, and, also, collateral branches of both the anterior and posterior perforating arteries.

3. Nonspecified vessels of the myocardium.

The left branch of the His bundle receives blood from three different groups of vessels:

1. An anastomotic plexus supplied by terminal branches of the ramus septi fibrosi, the ramus cristae supraventricularis, the ramus limbi sinistri, and many other small arterioles.

2. Other anterior and posterior perforating arteries.

3. Nonspecific arteries of the extraseptal myocardium which anastomose freely with each other.

By means of various technical improvements, the author demonstrates that all arteries which supply blood to the node of Tawara, the His bundle, and the branches of the bundle anastomose with each other, as well as with nonspecific arteries of the myocardium. These arteries, therefore, should be considered only as main arteries, and not as terminal vessels.

Both the main arteries and the anastomoses run in the same direction as the excitation wave of the myocardium.

The study is well presented, and will be of interest to many students of cardiology. The photographs are remarkable.

ALDO LUISADA.

American Heart Association, Inc.

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The American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The American Heart Journal is under the editorial supervision of the Association.

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The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

**Executive Committee.*

American Heart Journal

Vol. 27 February, 1944 No. 2

Original Communications

ORTHOSTATIC TACHYCARDIA AND ORTHOSTATIC HYPOTENSION: DEFECTS IN THE RETURN OF VENOUS BLOOD TO THE HEART*

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Lieutenant Colonel Edgar V. Allen, MC,
Army of the United States, and
Captain Thomas B. Magath, MC-V(S),
United States Naval Reserve

IN A previous paper[1] we demonstrated that failure of return of an adequate amount of venous blood to the heart is an essential factor in the syndromes of orthostatic hypotension and orthostatic tachycardia. When patients suffering from these disorders blow against a column of mercury, thus increasing the intrathoracic pressure† (Flack test), the venous return fails to the extent that there are a marked decrease of the filling of the heart, decreased cardiac output, and subsequent failure of the peripheral pulse. We were able to demonstrate that maintenance of the recumbent position potentiated defects of venous return in the erect state, and that the use of the "head-up" tilted bed frequently caused alleviation of both signs and symptoms. This observation has been confirmed recently by the work of Corcoran, Browning, and Page.[2] Since this first report we have enlarged our study and have made additional observations.

TECHNIQUE

During the past two years, normal subjects and a large group of patients who were suffering from a variety of disorders have been examined in a consistent, detailed manner with respect to standing and recumbent blood pressures, heart rates, and Flack tests. Multiple studies were done

Received for publication March 30, 1943.

*The opinions and assertions contained herein are the private ones of the writers, and are not to be considered as official, or reflecting the views of the Navy Department or the naval service at large.

†The lower lines in Figs. 1, 2, and 3 measure the pressure in the tube leading to the column of mercury against which the subject blows. The data, therefore, do not actually indicate intrathoracic pressure, although they give a rough measure of it.

on each patient over a period of several days, and at varying times. Heart rates which were normal in the recumbent position and which immediately increased to more than 120 beats per minute on the assumption of the erect posture were considered of significance only if they immediately reverted to normal when the recumbent position was resumed. Postural variations of blood pressure were considered abnormal only when very large, consistent reductions occurred when the erect posture was assumed, and when such reductions were associated with symptoms or with compensatory tachycardia and a positive Flack reaction.

A positive Flack reaction was considered to be one in which, when the subject was erect, the radial pulse disappeared within a period of ten seconds after the initiation of the blowing and did not return as long as the blowing could be maintained. Frequently, it was observed that there was a brief initial disappearance of the radial pulse, but that the pulse returned vigorously after a few seconds. Such a disappearance was not considered to be a positive reaction. Caution was used in describing as positive a blowing reaction which was not accompanied or immediately followed by faintness, blurring of vision, and other sensations of impending syncope. Some women and asthenic men were not able to blow the column of mercury to the 40 mm. mark. For these persons a 30 mm. blow was used as the standard. Since palpation of the radial pulse was not considered an entirely reliable index of peripheral pulsation, recordings of the pulse volume of the index finger were obtained by means of the finger plethysmograph through the medium of a rubber tambour, reflected light, and moving, sensitized paper. This method visualized the impressions obtained through the palpating finger in a qualitative manner. Quantitative measurements could not be applied to the results with our technique, and the results cannot be considered to be more accurate than impressions gained through simple palpation.

Crude as our attempts have been to measure the potential of venous return, it is apparent that gross defects in the return of venous blood to the heart can be appreciated by these simple methods.

CLASSIFICATION

Group 1. Inconsistent Orthostatic Failure of Venous Return.—Subjects in this classification may or may not demonstrate at any one time the classical signs and symptoms of failure of venous return in the erect posture, namely, orthostatic weakness, faintness, and occasional syncope, associated with orthostatic hypotension or tachycardia, and an abnormal Flack reaction. Both signs and symptoms disappear in the recumbent position. Hypotension, if present, is associated usually with compensatory tachycardia. There may be only tachycardia in the erect posture, associated occasionally with a fall in blood pressure or a diminution in pulse pressure. Both signs and symptoms are usually much worse in the morning, after the patient first gets out of bed, and quickly improve after the

subject continues to maintain the erect state. At times during the day an abnormal Flack reaction may be the only indication that the patient has a potential defect of venous return. In this group of persons the failure of venous return is not as a rule as severe as that encountered in Group 2, in which the failure is demonstrated consistently. Usually, no objective evidence of organic dysfunction of the autonomic nervous system can be demonstrated. The circulatory failure encountered in this inconsistent group appears to be associated with undue shifts of blood volumes and extracellular fluid gravitating to the lower extremities. The increased heart rates, low blood pressures, and abnormal Flack reactions can be abolished by the assumption of the recumbent position or by the application of tourniquets around the thighs. It has been our experience that the loss of volume of circulating blood through abdominal pooling appears to be a minor and relatively unimportant factor as compared with the loss related to the lower extremities.

A normal man may exhibit, at times, the signs and symptoms of failure of venous return. The margin between adequacy and incompetence is so narrow that, when a man stands erect without moving, he hovers on the verge of circulatory collapse.[3] Such failure may be precipitated by a variety of factors: exposure to heat, loss of blood, poor tone of striated muscle, psychic trauma, or the maintenance of a recumbent state for long periods. The effect of heat and the results of loss of blood and fluid have been the subject of many investigations, and it is not our purpose to review the venous return aspects of these disorders. Rather, we should like to emphasize the role of certain factors which appear to have been neglected.

Prolonged recumbency: In normal man there are functional disturbances of venous return which seem related solely to failure of the circulation to adapt quickly to the erect posture after the subject has been recumbent for a prolonged period. It is an everyday hospital experience to witness the rapid heart rates and low blood pressures of patients who are allowed to stand for the first time after protracted rest in bed. It is apparent that these patients have lost a measure of postural vascular stability, a loss which is expressed in their inability to stand without signs or symptoms. This maladaptation is functional, in that it is reversible. If such a patient continues to stand erect for longer and longer periods each day, vascular stability is regained. Through repeated exposures to gravitational pull, the body conditions itself to resist the effects of gravity entailed by the erect state. Any sudden increase of the resistance to venous return, such as is caused by the Flack test, may precipitate acute and sudden failure.

CASE 1.—An athlete, aged 17 years, was studied carefully in regard to heart rate, blood pressure, and Flack tests, for a week prior to an enforced period of rest in bed. No vascular abnormalities could be discovered. After four days of absolute rest in bed, he stood erect and the studies were repeated. No abnormal changes in heart rate and blood

pressure could be detected, but the Flack reaction was grossly abnormal. The pulse disappeared within the first few seconds of the blowing, and, at the expiration of the period, the subject developed syncope (Figs. 1 and 2).

Pregnancy: Orthostatic hypotensive tendencies, orthostatic tachycardia, and positive Flack reaction are observed commonly during and after pregnancy. The first three months of pregnancy are associated frequently with vomiting in the early part of the morning, and, in addition, with the signs and symptoms of orthostatic failure of venous return. There would appear to be a more than casual relation between the vomiting and the failure of venous return. Both have postural features, show morning exacerbation, and frequently undergo spontaneous remission during the course of the later months of pregnancy. After parturition, postural defects of venous return are observed frequently during convalescence.

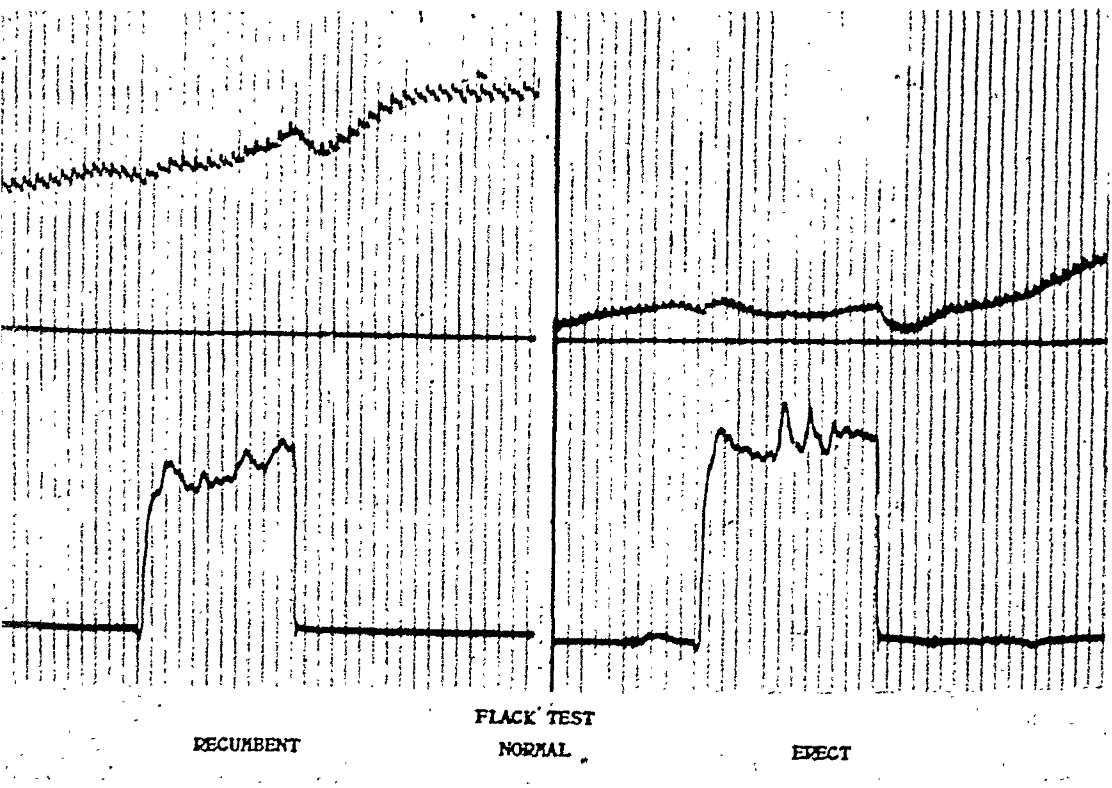

Fig. 1.—Recordings of volume of pulse by means of the finger plethysmograph (upper lines) and intrathoracic pressure (lower lines) during the Flack test before a period of rest in bed (control). During this control period the subject repeatedly did not exhibit any striking change in the radial or peripheral pulse while he was blowing in the recumbent and erect postures.

Case 2.—A normal woman, aged 32 years, was studied in regard to potentials of venous return throughout pregnancy. During the first three months of pregnancy she occasionally experienced nausea and vomiting in the early part of the morning. These symptoms occurred during the first half hour after arising in the morning, and were associated invariably with orthostatic tachycardia; the pulse rate varied

from 130 to 140 beats per minute. The Flack reaction was markedly positive. The heart rate and the Flack reaction immediately returned to normal in the recumbent state. From the fourth month to term, the gastrointestinal symptoms disappeared, no orthostatic vascular abnormalities could be detected, and the Flack reaction was normal. After an uneventful labor, orthostatic vascular studies were conducted during convalescence. When the patient first assumed the erect posture on the tenth day of convalescence, no abnormalities of heart rate or blood pressure could be detected for the first four minutes. During this period the Flack test was tried; the patient attempted to blow the column of mercury to a height of 40 mm. Her radial pulse disappeared during the

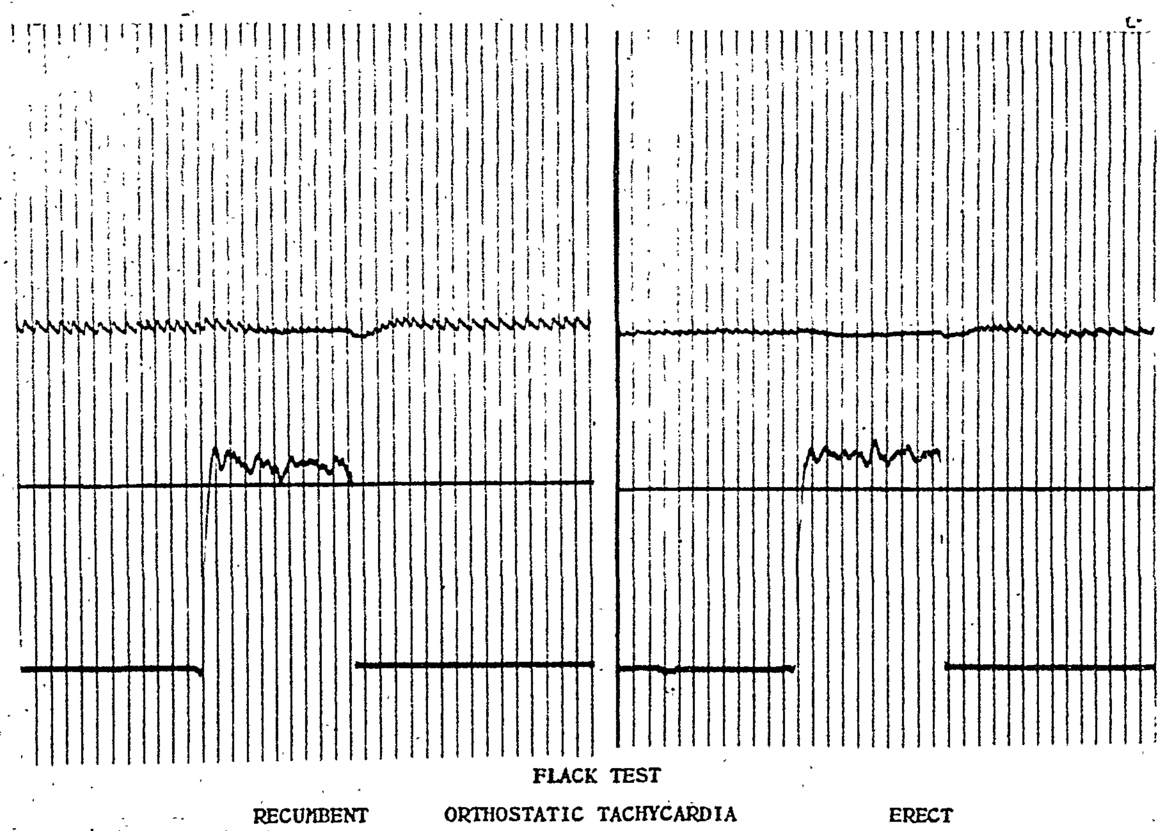

Fig. 2.—Recordings of volume of pulse by means of the finger plethysmograph (upper lines) and intrathoracic pressure (lower lines) during the Flack test after a four-day period of absolute rest in bed. In the erect posture the radial and peripheral pulse disappeared during the first few seconds of the blow. The patient fainted at the expiration of the test.

first few seconds of the blow, which she was able to maintain for only eight seconds before developing syncope. After repeated examinations it was discovered that, during the first forty-eight hours of being released from absolute rest in bed, orthostatic tachycardia and marked changes of pulse pressure would develop at the end of a four-minute period of standing. The Flack reaction was consistently positive. These abnormalities gradually disappeared during the following fourteen days. At any period, when tourniquets were placed around the thighs in the recumbent state, after which she was allowed to stand, the heart rate, blood pressure, and Flack reactions were normal. Abdominal compression did not have any effect on the failure of venous return (Fig. 3).

Psychic factors: It is well known that the autonomic nervous system plays a definite role in the maintenance of arteriolar tone. Attention has been focused almost exclusively on the nervous influences on the arterial side of the vascular tree, and the role of the autonomic nervous system in the maintenance of capillary-venous tone has been neglected. The work of Weiss, and others,[4, 5] in regard to the venous effects of shock induced by the administration of sodium nitrite, and our own experience with the gross defects of venous return after sympathectomy for essential hypertension called our attention to the fact that emotional circulatory disturbances might be related to disorders of the autonomic regulation of capillary venous return. Psychic syncope (fainting) seems to be one such disorder, in that it is postural and that the cerebral ischemia can be prevented by the recumbent state.

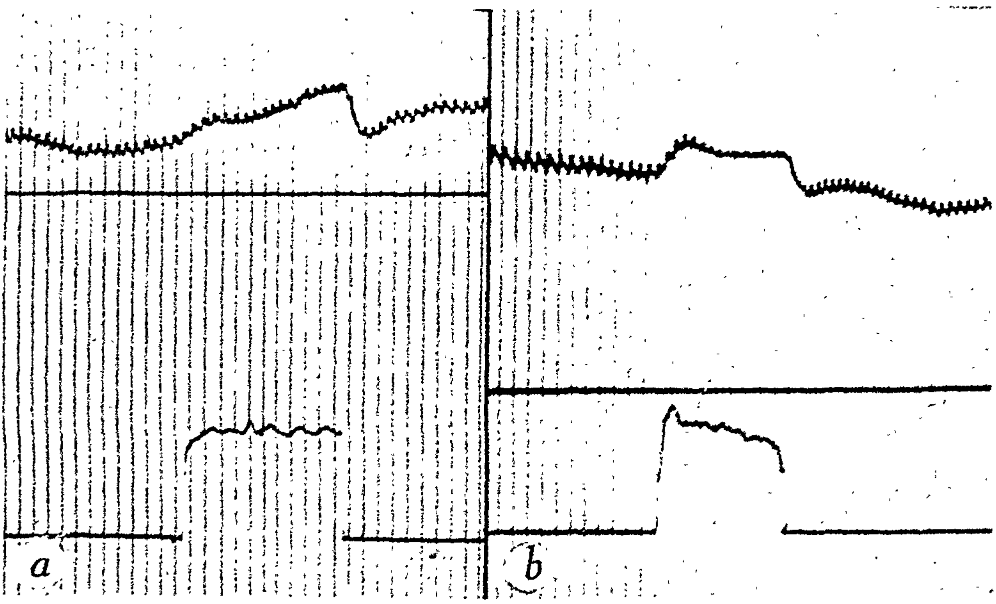

Fig. 3.—Volume of pulse of a pregnant woman recorded by means of the finger plethysmograph (upper lines) and intrathoracic pressure (lower lines) during the Flack test with subject in erect position. *a*, Control period at the sixth month of pregnancy; *b*, on first standing erect on the tenth post-partum day. The radial pulse disappeared and the patient fainted after eight seconds of increased intrathoracic pressure.

We have had the opportunity of measuring potentials of venous return by the Flack test in a group of 100 normal subjects who were awaiting venipuncture. Four subjects, at the end of one minute of standing, had heart rates of more than 120 beats per minute and positive Flack reactions. Immediately prior to venipuncture the tachycardia was orthostatic. Two subjects who had normal heart rates and blood pressures also had positive Flack reactions. During venipuncture, which was done with the subject in the erect posture, two subjects fainted: one who had orthostatic tachycardia and a positive Flack reaction, and one who had no tachycardia but a definite Flack

reaction. The remainder of the group did not have any untoward symptoms. The two patients who fainted recovered consciousness immediately on being placed in the recumbent position, but suffered repeated, partial, syncopal seizures when they attempted to rise during the first five minutes after the faint. One hour later, the standing heart rates fell within normal limits, but the Flack reaction remained positive during a period of forty-eight hours of observation. Obviously, gravity played a major role in the syncopal attacks of these two subjects, which were precipitated by a psychic stimulus.

Constitutional inferiority of venous return: Many patients who have defects of venous return fall into this classification. Frequently they are said to have neurocirculatory asthenia. Recognition of the essential nature of the disorder is uncommon. The signs and symptoms are orthostatic, and are characteristic of orthostatic failure of return of adequate amounts of venous blood to the heart. Frequently the subjects are tall, thin, and asthenic, or have suffered protracted loss of weight. The history is commonly that of exhaustion, weakness, faintness, and, occasionally, syncope in the erect posture, with relief in the recumbent position. Such patients are more likely than "normal" men and women to suffer debilities after long rest in bed or dehydration from heat, or subsequent to the use of alcohol or cathartics; the loss of tone of striated muscle results from lack of exercise, or from the psychic traumas of life. Orthostatic tachycardia and hypotension usually will be found only if such a person is examined when he is having symptoms. Blood pressures and heart rates must be taken in the erect posture and compared with those in the recumbent position. If the abnormalities are significant, and if the patient has a positive standing Flack reaction, deficiency of venous return is present.

Such patients frequently have psychoneuroses of varying degree. Anxiety states, associated with hyperventilation syndromes, are common. It has been suggested that the trigger which sets off such attacks of overbreathing may be traced frequently to a shift in the volume of circulating blood that is directly referable to defects of venous return. The anxiety experienced by these persons and the inability of their physicians to understand and explain their difficulties to them in a plausible manner result frequently in the establishment of a vicious circle of symptoms. It is often very difficult to ascertain whether psychoneurosis is the primary difficulty and the defect of venous return is the result of secondary inactivity and rest in bed, or whether the defect of venous return has resulted in psychoneurotic manifestations.

Remote disturbances of function, with venous return components: Abnormalities of potential of venous return can be measured by standing heart rates, blood pressures, and Flack tests in a variety of syndromes not usually associated with venous components.

Caloric and rotational stimulation of the vestibules of normal persons, varieties of seasickness and airsickness, the symptoms of which are postural, undue exposure to heat, abnormal loss of body fluid, and primary shock, with its nervous basis of pain and psychic factors, may bring out defects of venous return of varying degree which frequently play major roles in the total functional disability. In these conditions, the assumption of the erect posture may precipitate failure of venous return which is masked by the recumbent state.

Defects of venous return associated with organic disease: Poor mechanisms of venous return are associated frequently with debilitating diseases and with the convalescence of patients who have been bedridden for prolonged periods. In most instances the inconsistent nature of the orthostatic signs and symptoms suggests physiologic disturbances of a transient and secondary character which may include loss of tone of striated muscle of the lower extremities, changes of water balance, abnormal shifts of extracellular fluid, and other, little understood, secondary results of debility. On the other hand, some disease entities may be associated from the onset with severe, constant defects of venous return, usually accompanied by objective evidence of disorders of the autonomic nervous system which suggest a primary relation between the disease and the orthostatic defect of venous return. Examples of this latter group will be included in Group 2.

It is of interest that the presence of severe hypertension is compatible with abnormalities of venous return. Occasionally, large reductions of blood pressure, of more than 100 mm. Hg, are observed when a patient who has hypertension first stands erect after a period of rest in bed. Such changes of blood pressure are, as a rule, transient, lasting only a few seconds, but during this period the Flack reaction may be markedly positive, and returns to normal only when previous levels of blood pressure are established. Such transient reductions of blood pressure may explain the frequency of periods of unconsciousness which occur immediately after patients arise from bed, or when intrathoracic pressure is increased by straining at stool. A few seconds of diminished cardiac output in the presence of arterial hypertension may provoke gross vascular insults, resulting in ischemic syncope, cerebral thrombosis, or ischemic myocardial damage.

In summary, many syndromes present transient, inconsistent abnormalities of venous return, with remissions and exacerbations which cannot be controlled or foreseen adequately. It has been our experience that investigation of such cases in regard to causative factors, contributing disabilities, and the results of treatment cannot be conducted in a satisfactory manner, although insight may be gained into the nature of the disability. It is only when the venous return consistently fails in the erect posture that objective studies of an experimental nature may be conducted with profit.

Group 2. Consistent Orthostatic Failure of Venous Return.—Subjects in this classification consistently have severe orthostatic hypotension. Objective evidences of disorders of the autonomic nervous system are common: loss of sweating over large areas of the body surface, associated with intolerance to heat, frequent absence of compensatory reflex tachycardia, and impotence. Symptoms related to the deficit of venous return result from the erect posture only, and are relieved by recumbency or by removing the legs from the general circulation by means of tourniquets. The Flack reaction is invariably positive and dramatic, and frequently a deep inspiration will cause the peripheral pulse to disappear. The signs and symptoms show classical exacerbation in the morning, which is related to rest in bed. Remissions are rare.

In our experience the syndrome has affected patients who are suffering from tabes dorsalis, diabetic neuritis, the combined sclerosis of pernicious anemia, exophthalmic goiter, diabetes insipidus, disseminated sclerosis, hypopituitarism with chromophobe adenoma, and sprue. To this group belong those patients who suffer from idiopathic orthostatic hypotension for which no causative disease entity can be established. In addition, we believe that patients who have undergone extensive sympathectomy for hypertension may be classified as having a consistent orthostatic defect of venous return for a variable period after operation.

It is among this group of patients who have a consistent disorder that objective studies can be made which give insight into the whole problem of venous return. The results of such studies can be applied with advantage to normal subjects under vascular investigation and to patients who have inconsistent defects of venous return.

Such studies require careful controls, for wide variations of blood pressure, heart rate, and symptoms may occur. Defects of venous return in the erect posture are increased invariably by rest in bed, and, conversely, are improved after the patient has maintained the erect posture for a number of hours. The blood volume is also influenced by the maintenance of a fixed position of the body, and the hematocrit value may change. The external temperature, the hydration of the body, and the intervals between feedings should be constant if accurate determinations are to be made.

We are presenting a clinical study of observations under such controlled conditions on two patients who had marked, consistent defects of venous return, demonstrating the effect of a postural state on the potential of venous return and on the circulating blood volume, and also suggestive indications that an increased intake of sodium chloride may aid in the maintenance of postural vascular stability.

Both patients had disorders of the autonomic nervous system, in that there were absence of sweating and intolerance to heat. Both had relative hypochromic anemia, and their disorder of venous return was

of long standing. Both responded dramatically and consistently to a regimen of the "head-up" bed and increased intake of salt, and this improvement was reversible at the will of the examiner. In neither case do we suggest that we have established a cure. The treatment has been symptomatic.

CASE 3.—A farmer, aged 57 years, was seen first at the Mayo Clinic on Aug. 10, 1940, complaining of exhaustion, faintness, blurring of vision, and occasional syncope. These symptoms had been present since 1933, and had progressed to the point that he was unable to do his farm work. Syncopal attacks were precipitated by sudden change of posture and by lifting heavy objects. He had received several intramuscular injections of liver extract for his anemia, without benefit. On being questioned, the patient stated that his symptoms were always much worse in the morning, and that he improved progressively as the day advanced.

General physical examination did not reveal any abnormalities pertinent to his complaints, with the exception of mild hypochromic anemia, which was confirmed by examination of a blood smear. The concentration of hemoglobin was 12 Gm. per 100 c.c. of blood; the erythrocytes numbered 4,580,000, and the leucocytes, 5,000, in each cubic millimeter of blood. Free hydrochloric acid was obtained on analysis of gastric contents. The flocculation reaction for syphilis and roentgenograms of the chest and gastrointestinal tract were normal. No cause for the hypochromic anemia could be discovered. Postural vascular studies were found to give abnormal results, and the patient was hospitalized for detailed investigation. Rest in bed was allowed only during a period of nine hours at night. An ordinary diet, with 1,500 c.c. of fluid in twenty-four hours, was given.

Spontaneous variations of postural vascular adaptation: During a period of three days, observations on postural blood pressure and heart rate were conducted at various times during the day, and a definite variation of objective findings was found to coincide with alterations of symptoms. If the study was made before the patient had arisen in the morning, a marked defect of venous return was very apparent. When the patient was recumbent, his blood pressure was 130/80, and his heart rate, 84. When he had been erect for one minute his systolic blood pressure had decreased to 50 mm. Hg, his diastolic blood pressure could not be measured, and his heart rate had increased to 126. After three minutes in the erect position neither his blood pressure nor his heart rate could be measured and he was retching and semiconscious.

The Flack test, conducted with the patient erect, gave markedly positive results. On three separate occasions the patient became pulseless and fell to the floor unconscious within ten seconds of initiating an attempt to blow the column of mercury to a height of 30 mm. On one occasion convulsive twitchings occurred momentarily during the brief period of unconsciousness. If tourniquets were applied around the upper part of the thigh and constricted above the arterial blood pressure, and then the patient was allowed to stand erect, no fall in blood pressure occurred within a three-minute period, and the Flack reaction was normal.

If vascular studies were conducted in the afternoon, after the patient had been up and about, a definite change of postural vascular stability was evident. When he was recumbent, his blood pressure

averaged 142/72, and his heart rate, 62. When he had been erect for one minute, his blood pressure was 90/80, and his heart rate, 104. After three minutes in the erect position his blood pressure was 80/60, and his heart rate, 110. After ten seconds of standing running, his blood pressure was 66/38, and his heart rate, 110. During these periods the Flack reaction was positive. The patient would become pulseless when he tried to blow the column of mercury to a height of 30 mm., but would not develop syncope.

Sweating defects indicative of dysfunction of the autonomic nervous system were demonstrated over large areas of the trunk and lower extremities. The patient exhibited intolerance to heat. When he was placed in a hip bath in a sitting posture with the water at 108° F., the blood pressure fell within five minutes from 110/70 to 60/40. In twenty minutes the pulse and blood pressure were imperceptible, and the patient lapsed into syncope when taken from the bath. The blood pressure remained low for an hour, during which time the patient was unable to stand for longer than a minute without developing syncope.

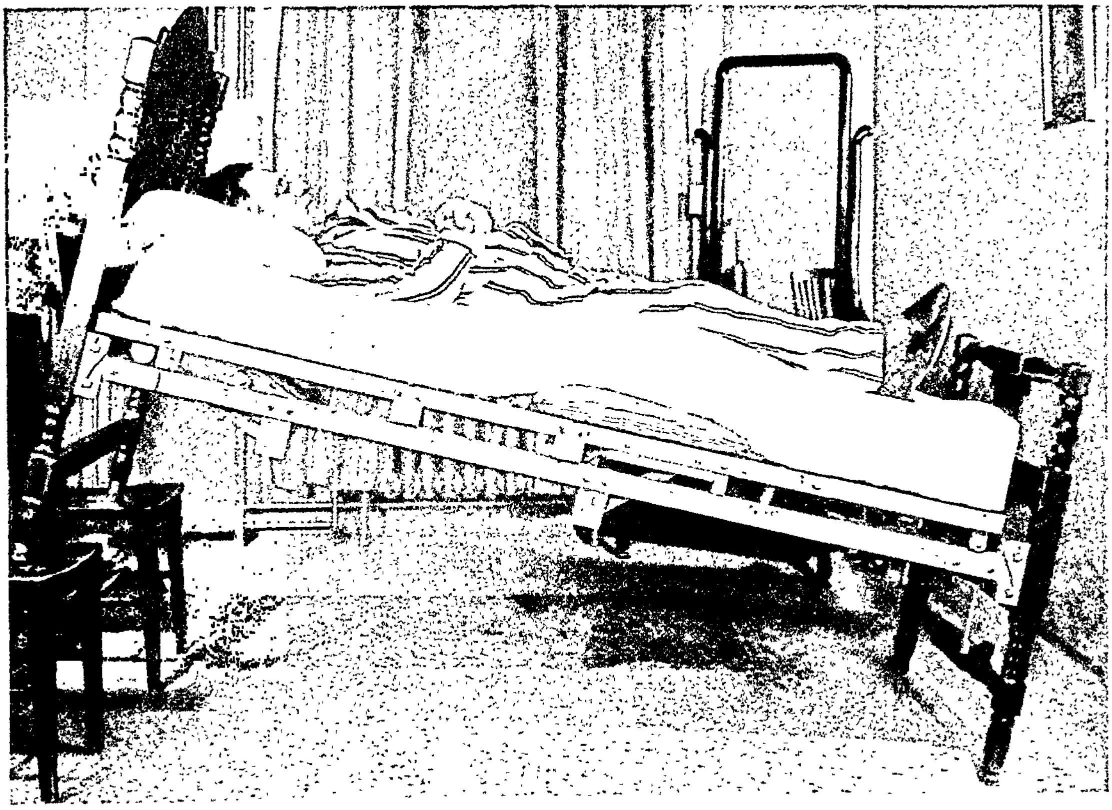

Fig. 4.—The "head-up" bed. The casters of the bed are removed and the posts of the head of the bed are placed on ordinary kitchen chairs, 16 to 18 inches (40 to 45 cm.) high. A hard pillow is placed under the mattress at the level of the thighs to prevent slipping. The head of the patient is elevated and the legs are dependent.

Effect of the "head-up" bed: The patient was then placed on a bed (Fig. 4), the head of which was elevated on two chairs to the height of approximately 16 inches (40 cm.). A pillow was placed under the mattress at the level of the thighs to prevent slipping. No other features of his care were altered. His fluid intake remained constant, and his period in bed was maintained at nine hours during the night. Striking improvement in the standing heart rate and blood pressure, and lessening of symptoms occurred within forty-eight hours. The following observations were conducted before the patient arose in the morning.

When he was recumbent, his blood pressure was 140/90, and his pulse rate, 74. After one minute in the erect position his blood pressure was 90/70, and his pulse rate, 118. After three minutes in the erect position his blood pressure and pulse rate were the same as after one minute. After five minutes his blood pressure was 90/72, and his pulse rate, 116. After ten minutes his blood pressure was 80/60, and his pulse rate, 114.

Effect of the "head-up" bed and increased intake of salt: The day after the foregoing observations, the patient, besides sleeping in the "head-up" bed at night, was given 12 Gm. of salt daily in addition to his diet, and his water intake was increased to 2,000 c.c. The next morning there was a distinct improvement in excess of that which occurred when he was using the "head-up" bed alone. This improvement was maintained for two days. The patient did not have any orthostatic symptoms during this forty-eight hour period, for which the average morning determinations were as follows: When he was recumbent, his blood pressure was 134/80, and his pulse rate, 72. After one minute in the erect position his blood pressure was 100/70, and his pulse rate, 80. After five minutes his blood pressure was 105/70, and his pulse rate, 86. After ten minutes his blood pressure was 100/72, and his pulse rate, 90. After fifteen minutes his blood pressure was 98/70, and his pulse rate, 104.

Effect of a flat bed with increased intake of salt: The intake of salt was maintained at 12 Gm. extra, daily, but the patient was allowed to sleep on a flat bed during a nine-hour period at night. The following morning there was a distinct change in both signs and symptoms when the patient first rose. When he was recumbent, his blood pressure was 130/70, and his pulse rate, 68. After one minute in the erect position his blood pressure was 65/55, and his pulse rate, 100. After three minutes his blood pressure was 80/60, and his pulse rate, 106. After five minutes his blood pressure was 60/40, his pulse rate was 114, and he felt faint.

When the patient was maintained on this regimen for two days there was no further significant change. The patient remained somewhat better with the increased intake of salt and the flat bed, but the improvement was not nearly as marked as on the combined regimen of increased intake of salt and the "head-up" bed.

Flat bed and normal intake of salt: The extra intake of salt was discontinued and the patient slept on a flat bed. Within forty-eight hours there was an increase in the signs and symptoms of failure of venous return, as indicated by the following studies, which were conducted before the patient arose from bed in the morning. When he was recumbent, his blood pressure was 138/80, and his pulse rate, 68. After one minute in the erect position, his systolic blood pressure was 50 mm. Hg, his diastolic blood pressure could not be measured, and his pulse rate was 126. After three minutes his blood pressure was not obtained; his pulse rate was 134. After five minutes his blood pressure was 58/50, and his pulse rate, 140; syncope occurred after this last reading.

The patient was then placed on a combined regimen of increased intake of salt of 6 Gm. daily in divided doses, and, in addition, the "head-up" bed at night. Within twelve hours there was again a dramatic improvement. The blood pressure approached normal limits in the erect posture and remained so. One month after dismissal the patient was requested by letter to try sleeping again on a flat bed,

and he reported that in twelve hours there was a return of all his symptoms. A letter received six months after his return home on a regimen of the "head-up" bed and increased intake of sodium chloride follows.

"Since returning home I have felt fine all the time with the exception of the first week. I have been able to do all the chores all the time and get along nicely provided I do not lift too hard or hurry too much. I feel reasonably sure that the 'head-up' bed has done wonders for me. I have gained 20 pounds [9.1 kg.], 10 pounds [4.5 kg.] more than I ever weighed in all my life." It seems probable that the increased intake of salt was also a factor in his gain of weight.

Comment on Case 3: Under controlled conditions this patient showed the effect of a preceding postural state on the heart rate, blood pressure, and symptoms. With the use of the "head-up" bed at night, on a regimen of increased intake of sodium chloride, striking, reversible improvement occurred repeatedly. The increased intake of sodium chloride was not of much practical avail as long as the patient slept on a flat bed. The "head-up" bed at night increased postural vascular stability to a definite degree, but the improvement was not as marked as with the combined use of the "head-up" bed and salt. On this regimen the patient showed improvement which was maintained consistently for six months. The treatment was symptomatic. No organic cause could be discovered to account for the defect of venous return, aside from the dysfunction of the autonomic nervous system, as demonstrated by the defects of sweating.

CASE 4.—A department store serviceman, aged 35 years, was seen first at the clinic in June, 1941, complaining of progressive fatigue, inability to concentrate, decreased ability to work, and decreased libido, since 1935. In 1938 he had noted frequent headaches in the early morning, which were relieved by salicylates. The patient had experienced frequent attacks of faintness since the age of 16 years, associated with weakness and blurred vision, and relieved on the assumption of the recumbent position. These attacks had increased in frequency in the preceding year and were associated occasionally with momentary unconsciousness.

General physical examination revealed a man whose physical appearance suggested that he was suffering from hypopituitarism. He was of asthenic build, with soft, finely wrinkled skin. His face was pale and the growth of his beard was scanty. Growth of axillary and pubic hair was normal. The concentration of hemoglobin was 11.6 Gm. per 100 c.c. of blood; the erythrocytes numbered 4,210,000, and the leucocytes, 11,100, in each cubic millimeter of blood. Urinalysis, flocculation tests for syphilis, and roentgenograms of the chest, kidneys, ureters and bladder, and gallbladder gave normal results. The fasting concentration of sugar was 87 mg. in 100 c.c. of blood, and the basal metabolic rate was –5 per cent. A roentgenogram of the head revealed a Grade 2 enlargement of the sella turcica. There was a suggestion of erosión of the floor and posterior clinoid processes. A detailed examination of the eyes revealed 6/6 vision bilaterally. The fundi were negative. The optic disks were outlined clearly and of good color. Examination of the visual fields on the perimeter and tangent screen revealed a bitemporal depression which could be demonstrated only with the 1/1,000 bead. Neuro-

logic examination gave essentially negative results in the motor, sensory, and reflex fields.

A diagnosis of pituitary tumor, probably chromophobe adenoma, was made. Because of the minimal ocular changes, the protracted history, and the limited progression of symptoms, a course of roentgen therapy was advised, followed by a detailed re-examination several months later to ascertain whether any progression was evident.

The patient returned in August, after two courses of roentgen treatment had been given to the head. He had lost much ground in the interim, was much weaker and unable to work. The symptoms of exhaustion were very severe in the morning hours, and syncope was frequent. The concentration of hemoglobin was 10.6 Gm. per 100 c.c.; the erythrocytes numbered 3,540,000 in each cubic millimeter of blood. The basal metabolic rate was −8 per cent. Roentgenograms of the head and examination of the visual fields did not reveal any changes. It was evident on this examination that the patient's symptoms were out of all proportion to the physical signs, and because of the prominence of syncopal attacks, controlled studies were made of the heart rate and blood pressure. Orthostatic tachycardia and hypotension were evident and dramatic.

Each of the following studies was made under identical conditions, in the morning before the patient arose after nine hours of rest in bed. The patient received a standard diet and a controlled intake of water. The observations were made before breakfast. He was out of bed and active during the day. The average values obtained during a control study, lasting three days, were as follows: When the patient was recumbent, his blood pressure was 100/62, and his pulse rate, 92. After one minute in the erect position his blood pressure was 80/60, and his pulse rate, 156. After five minutes neither his blood pressure nor his pulse rate could be obtained, and he fainted. The Flack reaction was repeatedly positive. When performing the standing 30 mm. blow, the patient became pulseless and developed syncope within a ten-second period. In the recumbent state the patient could maintain the mercury at the 40 mm. mark for ten seconds without symptoms.

Orthostatic studies with the legs removed from the general circulation: With the patient recumbent, blood pressure cuffs were placed high up on the thigh of each leg and inflated to a pressure of 220 mm. Hg. The patient was then allowed to stand erect. When he was recumbent, his blood pressure was 98/60, and his heart rate, 86. After one minute in the erect position his blood pressure was 90/76, and his heart rate, 100. After five minutes his blood pressure was 96/80, and his heart rate, 100.

The cuffs were then released. Immediately the systolic blood pressure decreased to 50 mm. Hg, the diastolic pressure could not be measured, and, within thirty seconds, the patient fell unconscious. During the period of inflation of the cuffs, the patient was able to maintain the mercury at the 40 mm. mark while performing the Flack test standing, with no symptoms.

The effects of paredrinol sulfate and ephedrine sulfate by mouth: After the oral administration of 40 mg. of paredrinol sulfate (α-N-dimethyl-p-hydroxyphenethylamine sulfate), measurements of the blood pressure were made every fifteen minutes for an hour, and then every half hour for another hour. No distinct changes were noted. One and a half hours after he took the drug, the following studies were made. When the patient was recumbent, his blood pressure was 94/64, and his heart rate, 80. After one minute in the erect position his blood pressure was

68/54, and his heart rate, 132. After three minutes his blood pressure was 56/46, and his heart rate, 136.

Twenty-five minutes after the oral administration of ¾ grain (0.05 Gm.) of ephedrine sulfate, the following record was obtained. When the patient was recumbent, his blood pressure was 100/64, and his heart rate, 72. After one minute in the erect position his blood pressure was 76/58, and his heart rate, 96. After five minutes his blood pressure was 82/58, and his heart rate, 124. After seven minutes his blood pressure was 86/62, and his heart rate, 116. After ten minutes his blood pressure was 84/58, and his heart rate, 120.

This very definite improvement lasted for two hours, and the patient was able to stand quite well for periods of ten minutes without the signs or symptoms of impending syncope. The patient then reverted to his previous state. Additional studies after the oral administration of 0.75 Gm. of guanidine sulfate and the subcutaneous injection of prostigmine sulfate did not show any significant change in postural vascular stability.

Effect of the "head-up" bed: The head of the bed on which the patient slept at night was elevated to a height of 16 inches (40 cm.). No other factor in his management was changed. Studies of the blood pressure and heart rate were conducted at the same time as on previous occasions, before the patient rose in the morning. A very distinct change became evident overnight. On the first day, when the patient was recumbent, his blood pressure was 100/64, and his heart rate, 84. After one minute in the erect position his blood pressure was 92/64, and his heart rate, 108. After five minutes his blood pressure was 92/68, and his heart rate, 116. After ten minutes his blood pressure was 84/66, and his heart rate, 128. After eleven minutes his blood pressure was 64/50, his heart rate was 112, and he was experiencing the prodromal symptoms of syncope.

On the second day, when the patient was recumbent his blood pressure was 102/70, and his heart rate, 62. After one minute in the erect position his blood pressure was 84/70, and his heart rate, 88. After five minutes his blood pressure was 88/68, and his heart rate, 94. After ten minutes his blood pressure was 80/68, and his heart rate, 108. After fifteen minutes his blood pressure was 74/64, and his heart rate, 120.

On the third day, when the patient was recumbent his blood pressure was 104/64, and his heart rate, 68. After one minute in the erect position his blood pressure was 84/64, and his heart rate, 88. After five minutes his blood pressure was 84/70, and his heart rate, 106. After ten minutes his blood pressure was 82/68, and his heart rate, 96. After fifteen minutes his blood pressure was 84/66, and his heart rate, 106. After twenty minutes his blood pressure was 86/66, and his heart rate, 104. After twenty-five minutes his blood pressure was 62/48, his heart rate was 120, and he was feeling faint.

During the third and fourth days the patient had very little feeling of exhaustion, and stated that he felt better than at any time in the previous five years.

Effect after sleeping on a flat bed: To ascertain whether or not the improvement had been a mere coincidence, the patient was again placed on a flat bed at night. Nothing else was changed in his management. The following morning the patient had reverted to the same state as before treatment was initiated. When he was recumbent, his blood pressure was 94/74, and his heart rate, 82. After one minute in the

erect position his blood pressure was 74/64, and his heart rate, 120. After three minutes his systolic blood pressure was 50 mm. Hg, his diastolic blood pressure could not be measured, his heart rate was 150, and he fainted.

Effect of "head-up" bed and increased intake of salt: The patient then slept on the "head-up" bed at night and was given 9 Gm. of salt daily in addition to his diet. Within twenty-four hours he could stand erect for twenty minutes without syncope. When he was recumbent, his blood pressure was 110/68, and his heart rate, 82. After one minute in the erect position his blood pressure was 110/62, and his heart rate, 102. After five minutes his blood pressure was 98/66, and his heart rate, 112. After fifteen minutes his blood pressure was 88/64, and his heart rate, 112. After twenty minutes his blood pressure was 80/60, and his heart rate, 120. After twenty-five minutes his blood pressure was 60/30, his heart rate was 124, and he felt faint.

Effect of increased intake of salt and administration of desoxycorticosterone acetate, with the patient sleeping in a horizontal position: Immediately after the foregoing study, the increased intake of salt was maintained, but the patient was allowed to sleep on a flat bed at night. In addition, intramuscular injections of 5 mg. of desoxycorticosterone acetate were given daily. As a result of the cessation of sleeping in the "head-up" bed, in spite of the foregoing measures, a distinct change was noted the following morning. When the patient was recumbent, his blood pressure was 110/64, and his heart rate, 86. After one minute in the erect position his blood pressure was 86/68, and his heart rate, 116. After five minutes his blood pressure was 84/58, and his heart rate, 130. After nine minutes his blood pressure was 64/50, his heart rate was 120, and he felt very faint.

On the third day the increased intake of salt and the injections of desoxycorticosterone acetate were continued. The patient continued to sleep on a flat bed . On this day an oral temperature of 101° F. developed. When the patient was recumbent, his blood pressure was 112/62, and his heart rate, 88. After one minute in the erect position his blood pressure was 98/78, and his heart rate, 120. After three minutes his blood pressure was 65/38, his heart rate was 124, and he fainted.

On the fourth day the patient's temperature was normal. He appeared to have an infection of the upper part of the respiratory tract. Vascular stability was poor in spite of an apparent increase of blood volume and extracellular fluid. (This will be discussed later.) When he was recumbent, his blood pressure was 112/74, and his heart rate, 72. After one minute in the erect position his blood pressure was 88/58, and his heart rate, 102. After five minutes his blood pressure was 80/58, and his heart rate, 112. After six minutes his blood pressure was 45/24, his heart rate was 100, and he fainted.

Because of the patient's cough and feeling of malaise the study was terminated. Therefore, no definite conclusions were possible in regard to the effects of increased intake of salt and the administration of desoxycorticosterone acetate, although the indications were that they had very little effect on postural vascular stability. The patient was dismissed with instructions to take 6 Gm. extra of salt daily, and to sleep in a "head-up" bed. He was told to return for further investigation in three months. At the end of this time he had reported by letter that he had returned to work and was feeling better than he had felt in ten years. Further studies have been impossible.

COMMENT ON A STUDY OF TWO CASES

The foregoing clinical observations on these two patients and our previous studies of the syndromes of orthostatic hypotension and tachycardia associated with organic disease demonstrate several important principles:

1. Orthostatic hypotension and tachycardia are, in a secondary sense, disorders of venous return. The defect of venous return becomes evident in a very short time after the erect posture is attained, and, conversely, adequate circulation and a normal heart rate and blood pressure immediately follow the resumption of the recumbent position.

2. The site of this disorder appears to be the capillary-venous bed of the lower extremities, for the orthostatic symptoms and signs and positive Flack reactions are abolished when the lower extremities are separated from the general circulation by cuffs inflated about the thighs.

3. The circulatory defect caused by inadequate venous return in the erect state is either a direct result of pooling of abnormal quantities of blood in the lower extremities, or a result of a very rapid transudation of circulating fluid into the tissues of the lower extremities. The rapidity of the onset of the deficiency when the upright position is assumed, and the instantaneous recovery in the recumbent state suggest strongly that the defect is the result of pooling of blood in the capillary-venous bed itself.

4. It is apparent from our studies that the variations of potential of venous return occur in normal subjects and in patients who are suffering from a variety of disorders. A persistently maintained recumbent state enhances defects of venous return when the erect posture is assumed again. A persistently maintained, erect or semierect posture definitely lessens orthostatic changes in pulse rate and blood pressure, and increases postural vascular stability. This improvement in vascular adaptation depends on physiologic factors which are little understood.

5. It would appear that part of the postural vascular adaptation depends on physical mechanisms which are related to shifts of extracellular fluid and changes of blood volume.

Maintenance of the erect or semierect position favors the accumulation of additional extracellular fluid in the legs. We have observed frequently among patients who have been treated on the "head-up" bed that the appearance of early edema of the lower extremities coincides with lessening of the orthostatic signs and symptoms. This edema quickly disappears as the patients become more active. Such an increase of extravascular fluid might well act as a splint of the capillary-venous bed of the lower extremities, and prevent excess pooling of blood in the erect state.

Maintenance of the erect or semierect position favors the accumulation of blood itself in the legs, and the volume of circulating blood in the upper portions of the body is to that extent reduced. This loss of

volume of circulating blood in the upper part of the body should stimulate recovery mechanisms, as would an actual hemorrhage, by reduction of the capacity of the vascular bed by vasoconstriction, retention of body fluid, and interchange of fluid between tissues and vessels. If, through such recovery mechanisms, the volume of circulating blood in the upper part of the body approaches normal, then the assumption of the recumbent posture would gravitate additional volumes of blood into the circulation. This additional volume of blood could come from the vessels of the dependent portions of the body, or from the extracellular fluids accumulated there.

Measurements* of blood volume on three patients who were suffering from defects of venous return have suggested that maintenance of the "head-up" position results in an average increase of 500 c.c. of circulating blood. Repeated studies on one patient in this report (Case 4) indicate that his improvement was associated with a similar increase in blood volume.

CONTROL STUDIES OF BLOOD VOLUME IN CASE 4

Before breakfast, after the patient had slept nine hours on a flat bed, the recumbent blood pressure was 100/62, and the heart rate, 92. The venous return in the erect posture was very poor, and the patient could not stand more than five minutes before syncope occurred. The studies of blood volume were done with the patient *recumbent,* with the following results: His body weight was 86.2 kg.; the reading of the hematocrit was 35.5 per cent; the concentration of plasma chlorides was 99.3 milliequivalents per liter of plasma; the concentration of protein was 6.40 Gm. per 100 c.c. of plasma; the volume of plasma was 3,326 c.c., or 38.6 c.c. per kilogram of body weight; the volume of blood was 5,157 c.c., or 59.8 c.c. per kilogram of body weight; and the extracellular fluid amounted to 21.3 liters, or 2.47 per cent of the body weight.

Studies of Blood Volume After the Patient Had Slept in the "Head-up" bed.—The patient then slept on the "head-up" bed for two nights. On the third day there was great improvement. The patient was able to stand for twenty minutes; his blood pressure at the end of this time was 86/66, and his heart rate was 106. There was slight pitting edema of the lower extremities. The head of the bed was lowered, and studies of blood volume with the patient in the *recumbent* position were made immediately. The body weight was 87.1 kg.; the reading of the hematocrit was 34.8 per cent; the concentration of chlorides was 103.8 milliequivalents per liter of plasma; the concentration of protein was 6.45 Gm. per 100 c.c. of plasma; the volume of plasma was 3,743 c.c., or 43.0 c.c. per kilogram of body weight; the volume of blood was 5,741 c.c., or 65.8 c.c. per kilogram of body weight; and the extracellular fluid amounted to 22.2 liters, or 2.54 per cent of the body weight.

These studies appear to demonstrate an increase in total blood volume (about 600 c.c.) and an increase of the volume of extracellular fluid (about 900 c.c.) as a result of sleeping in the "head-up" position. Further studies are admittedly necessary, but have not been possible because of our entrance into military service.

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*The Evans blue technique was used for these measurements. The bromide technique was used for studying the quantity of extracellular fluid.

CONCLUSIONS

1. Orthostatic defects of venous return have been divided into two groups, namely, those in which orthostatic changes are inconsistent and are not associated in a primary sense with organic disease, and those in which orthostatic changes are consistent and are associated with organic changes.

2. Two cases of organic orthostatic defects of venous return have been studied clinically with respect to the effect of preceding postural states and the intake of excess amounts of sodium chloride. The use of the "head-up" bed and extra salt appears to result in definite symptomatic and objective changes which are reversible.

3. Studies suggest that the improvement resulting from the "head-up" bed and increased intake of salt corresponds to an increased volume of circulating blood and an increase of the extracellular fluid of the lower extremities.

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ELECTROCARDIOGRAPHIC CHANGES (LOCAL VENTRICULAR ISCHEMIA AND INJURY) PRODUCED IN THE DOG BY TEMPORARY OCCLUSION OF A CORONARY ARTERY, SHOWING A NEW STAGE IN THE EVOLUTION OF MYOCARDIAL INFARCTION

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THE kind of abnormal T deflections that are ascribed to local prolongation of the effective duration of the excited electrical state in cardiac muscle perifocal to an infarct,[1] or to perifocal ischemia of an infarct,[2, 3] has long been recognized[4] as the final stage of the temporary changes in the electrocardiographic evolution of myocardial infarction. Several years ago one of us (R. H. B.) concluded from theoretical considerations that the same kind of T deflections should likewise introduce the electrocardiographic evolution of myocardial infarction. Several clinical experiences, one of which has been reported,[2] have tended to confirm this opinion. Nevertheless, it is generally held that striking RS-T junction displacements introduce the electrocardiographic evolution of myocardial infarction.[5-8] The RS-T junction displacements have been ascribed to the fact that muscle at the periphery of the infarct acts as if it were in the electrically injured state,[9] or to muscle throughout which there exists during diastole, and again during systole, a gradient in the intensity of subnormal polarization, and throughout which the polarity of subnormal polarization is reversed temporarily during systole.[3] Under the latter circumstances, in the absence of the introduction during diastole into the body-galvanometer circuit of a current to neutralize the flow of the current of injury, the effect on the completed record is a displacement of the RS-T junction and the diastolic base line in opposite directions. The following is a preliminary report on the method devised to test the foregoing concepts and on the results obtained from its use.

METHOD AND MATERIAL

A moderately large dog (9 to 16 kilograms) is anesthetized by an intravenous injection of pentobarbital sodium (nembutal). The chest and left foreleg are shaved and the animal is placed in the right lateral position on the operating table. The right arm terminal of an Einthoven galvanometer is connected to the left foreleg through a nonpolarizable

Presented at a New Orleans meeting of the American Federation for Clinical Research, April 28, 1943.
Received for publication March 20, 1943.
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electrode. The left arm terminal of the galvanometer is connected to the exploring electrode through a similar nonpolarizable boot. The animal is given air through a tracheal tube with a positive pressure respirator, and the pleural cavity is opened through a 6 cm. incision at the level of the fourth or fifth intercostal space. The middle and lower lobes of the lung are retracted, exposing the left lateral aspect of the pericardial sac. A pad of cotton, 2 to 3 cm. in diameter, and moist with mammalian Ringer's solution, is placed on the strictly anterior surface of the pericardial sac close to the apex of the left ventricle. A wick of cotton fibers, drawn from the margin of the pad and connected with the boot electrode which receives the left arm terminal of the galvanometer, serves as the exploring contact. A control curve is recorded. The pericardial sac is opened through a 1.5 to 2 cm. incision in the region of the tip of the left auricular appendage. A small segment (3 to 6 mm.) of the anterior descending branch of the left coronary artery is gently dissected. No blood is permitted to enter the pericardial sac. A No. 1 linen suture 20 cm. long is passed under the artery without compressing the vessel, and its ends are loosely retained for subsequent closure of the artery. A second control curve is recorded and compared with the first control curve. If the control curves differ only in the form of the T deflection, the preparation is regarded as successful. A large, inverted T deflection in the first control is probably abnormal, and the preparation is likely to prove unsatisfactory. If the second control shows displacement of the RS-T junction in addition to an inverted T, the preparation is regarded as unsuccessful. At the present time we have experimented with five successful preparations (Dogs 1, 4, 7, 10, and 12).

Each experiment consists of making a continuous recording before, during, and after complete, temporary occlusion of the dissected arterial segment produced by retraction of the suture. The duration of the occlusions has varied in different instances from 30 seconds to 30 minutes. We have been able to perform as many as five or six experiments on a single preparation. The hearts were later inspected and were found to be normal in appearance.

RESULTS

Two typical patterns were obtained in twenty-odd experiments. One, the positive T pattern, was yielded by dogs 1 and 10, whereas Dogs 4 and 7 showed negative T patterns. In the former patterns the T deflections were positive in both controls. In the latter patterns, the T deflections were positive before, and negative after, arterial dissection (Fig. 1, *a* and *b* and Fig. 2, *a* and *b*).

Within three to four seconds after occlusion commenced, the T deflections which were positive before occlusion became sharply inverted, and reached maximal inversion in about 20 to 25 seconds (Fig. 1, *c*, *d*, and *e*). The T deflections which were inverted before occlusion became more deeply inverted, and reached maximal inversion in about 20 to 25 seconds (Fig. 2, *c* and *d*). These changes were followed by a progressive diminution of amplitude of the T deflections. Concurrently, the initial T segments progressed into rounded upward movements (Figs. 1, *f* and 2, *e*).

In part concurrent, and trailing, these changes, the RS-T junctions and the diastolic base line segments became progressively displaced in opposite directions, the former upward and the latter downward. With clocklike precision, striking RS-T junction displacements and upward peaking of the T deflections had developed gradually by the end of one and one-half minutes after the onset of occlusion. In the majority of

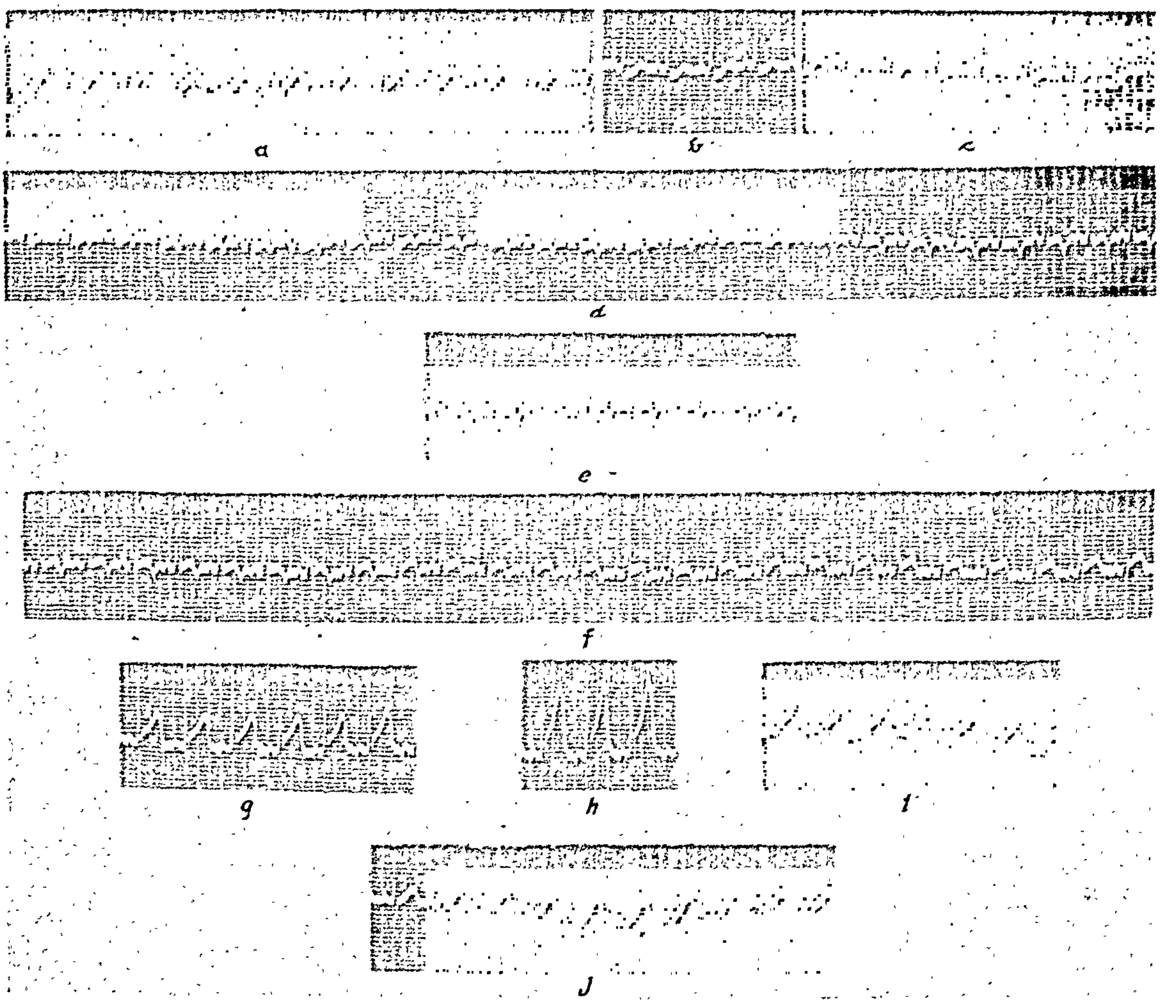

Fig. 1.—Selected recordings from a continuous curve taken before, during, and after a one and one-half minute occlusion of the anterior descending branch of the left coronary artery of Dog 1. The exploring electrode was on the strictly anterior aspect of the pericardial sac. Curves *a* and *b* are controls recorded before and after dissection of the artery. Occlusion commenced at the signal between *b* and *c*. Occlusion ended between strips *h* and *i*. The important features of the positive T pattern are shown. The time lines are 1/10 second apart. Standardization is approximately 1/3 normal. See text.

our experiments, the occlusion was suddenly released at this stage (Figs. 1, *h* and 2, *i*). Whether the occlusion was relatively long (3 or 5 minutes) or short (less than 2 minutes), the striking RS-T junction displacements and the displacements of the diastolic base line vanished within 5 to 7 seconds after cessation of occlusion (Fig. 2, *j*). Concurrently, the large, positive T deflections became greatly reduced in amplitude. In the positive T patterns, the positive T deflections remained

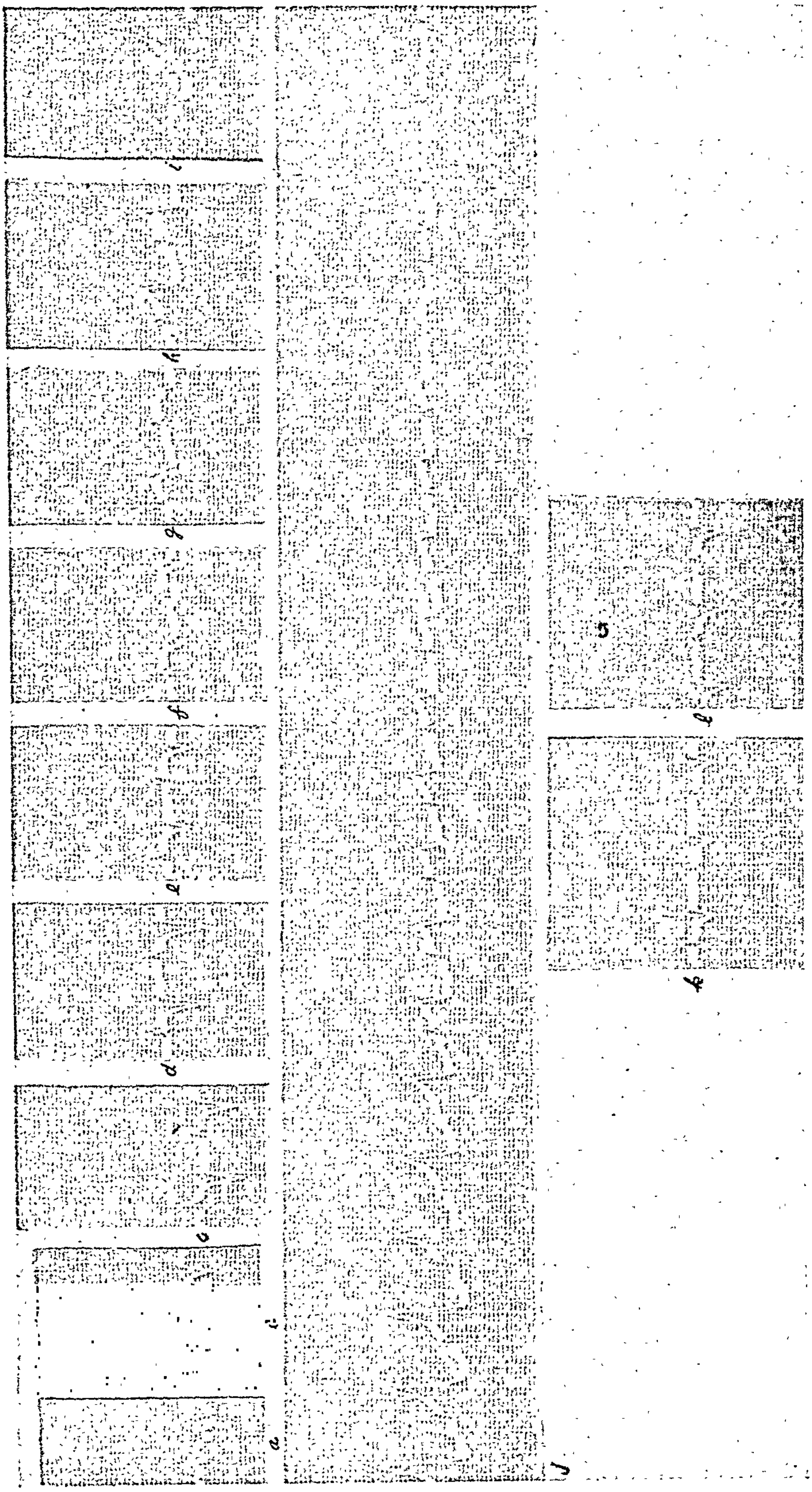

Fig. 2.—Selected recordings from a continuous curve taken before, during, and after a one and one-half minute occlusion (as described for Fig. 1) on Dog 7. Occlusion commenced between strips *b* and *c*. Occlusion ended at the commencement of strip *j*. Strip *l* was inscribed two minutes after occlusion ended. The important features of the negative T pattern are shown. The time lines are 1/10 second apart. Standardization is approximately 2/3 normal. See text.

positive after occlusion (Fig. 1, *j*). In the negative T patterns, the positive T deflections that were present at the cessation of occlusion gradually returned to their initially negative form in 5 to 10 minutes or less (Fig. 2, *k*). Thus, each pattern ended with a form of T similar to that which was present before occlusion. In the final stages of the positive T patterns obtained by repeated occlusions on the same preparation over a period of several hours, the T deflections developed negative terminal dips. Under similar circumstances, the final stages of the negative T patterns showed T deflections of somewhat greater amplitude (Fig. 2, *l*). In one experiment, a preparation which initially yielded negative T patterns was made to yield patterns of the positive T variety by an intravenous injection of 0.12 Gm. of theophylline with ethylene diamine.

A series of identical atypical patterns was recorded from one dog with an unusually rapid heart rate. These were of the positive T variety, but failed to display the inverted T phase immediately after occlusion.

CONCLUDING REMARKS

A method is described which permits observation of the complete electrocardiographic evolution of the development and cessation of acute local ventricular ischemia and injury. In all important respects the changes resemble the transitory and much more lengthy electrocardiographic evolution which is encountered during the course of myocardial infarction. Inasmuch as no infarction is developed during the recording of the ischemia and injury pattern, a clear demonstration is made of the kind of electrocardiographic changes which are routinely associated with myocardial infarction, but which neither depend upon the presence of infarction nor necessarily indicate its presence.

Contrary to general opinion, the ischemic T-wave changes constitute the first stage in the electrocardiographic evolution of myocardial infarction, as well as the last transitory stage. The RS-T junction and the diastolic base line displacements are best studied in that part of the ischemia-injury pattern which immediately follows cessation of occlusion (Fig. 2, *j*). The form observed strongly supports the explanation given elsewhere[3] of the electrical nature of cardiac muscle in the injured state.

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THE GRAPHIC REGISTRATION OF VENOUS PRESSURE TAKEN BY THE DIRECT METHOD

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TECHNICAL difficulties may partially account for the fact that there are few studies of directly measured and graphically recorded venous pressure in human beings. The main obstacle appears to be lack of a suitable mechanical recording device which will register pressures in millimeters of water and also be adaptable to a sterile technique.

Illustrative of one recording principle is the spirometer-like arrangement used by Kendrew.[1] In this apparatus most of the system is liquid filled, but an air pocket under the recording spirometer precludes absolute values, and the method indicates relative changes only. Doupe, et al.,[2] suggest an excellent and apparently highly sensitive method, using a T tube manometer. There is a rubber tube from the top of the inverted T manometer to a rubber diaphragm which carries a mirror for optical recording. This system allows for calibration, but, owing to the compressibility of the air column from manometer to mirror, the recorded changes are relative. A camera is necessary for this method. Recently, Feitelberg[3] has suggested a photoelectric recorder for biologic purposes which is probably adaptable to the recording of human venous pressure, but this apparatus seems more expensive and complicated than it should be for clinical work. The Hamilton manometer[4] meets all the requirements of accuracy for a direct graphic record of venous pressure, and has been used for this purpose with excellent results.[5] This equipment is bulky, requires a relatively expensive camera, and has not seemed suitable to us for use on the wards.

It is the purpose of this brief report to describe a simple piece of apparatus which can be easily assembled in any hospital laboratory. A convenient adaptation is a sensitive, float-recording manometer which is suitable for pressures of the order required. The apparatus is arranged so that only a portion of it need be sterilized. Venous pressure is recorded on a smoked drum, and a nonrecording water manometer is included in the system to verify values recorded on the drum. The recording manometer may be accurately calibrated, and pressure changes are recorded by a system entirely filled with liquid. Finally, the apparatus may be placed on a table and rolled about as desired.

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Received for publication March 27, 1943.

The arrangement of the recording device is shown in Fig. 1. The essential features are:

A, A 10 c.c. syringe, filled with 2 per cent sodium citrate solution and 100 units of heparin (Connaught). Part of the 10 c.c. is used to fill the distal portion of tubing which leads to the needle, and the remainder is used during the experiment to prevent clotting.

B, The usual water (citrate) manometer, placed in the system with T tube for convenience in obtaining correct zero level, sight readings during the experiment, and calibration.

C, Thin latex balloon separating sterile (left) and nonsterile (right) apparatus. This balloon must be partially collapsed after system is entirely filled with liquid, for distension or total collapse fails to transmit pressure accurately. This bottle and balloon may be reversed in direction and placed between syringe, *A,* and T tube leading to *B,* thereby further reducing amount of apparatus that must be sterilized.

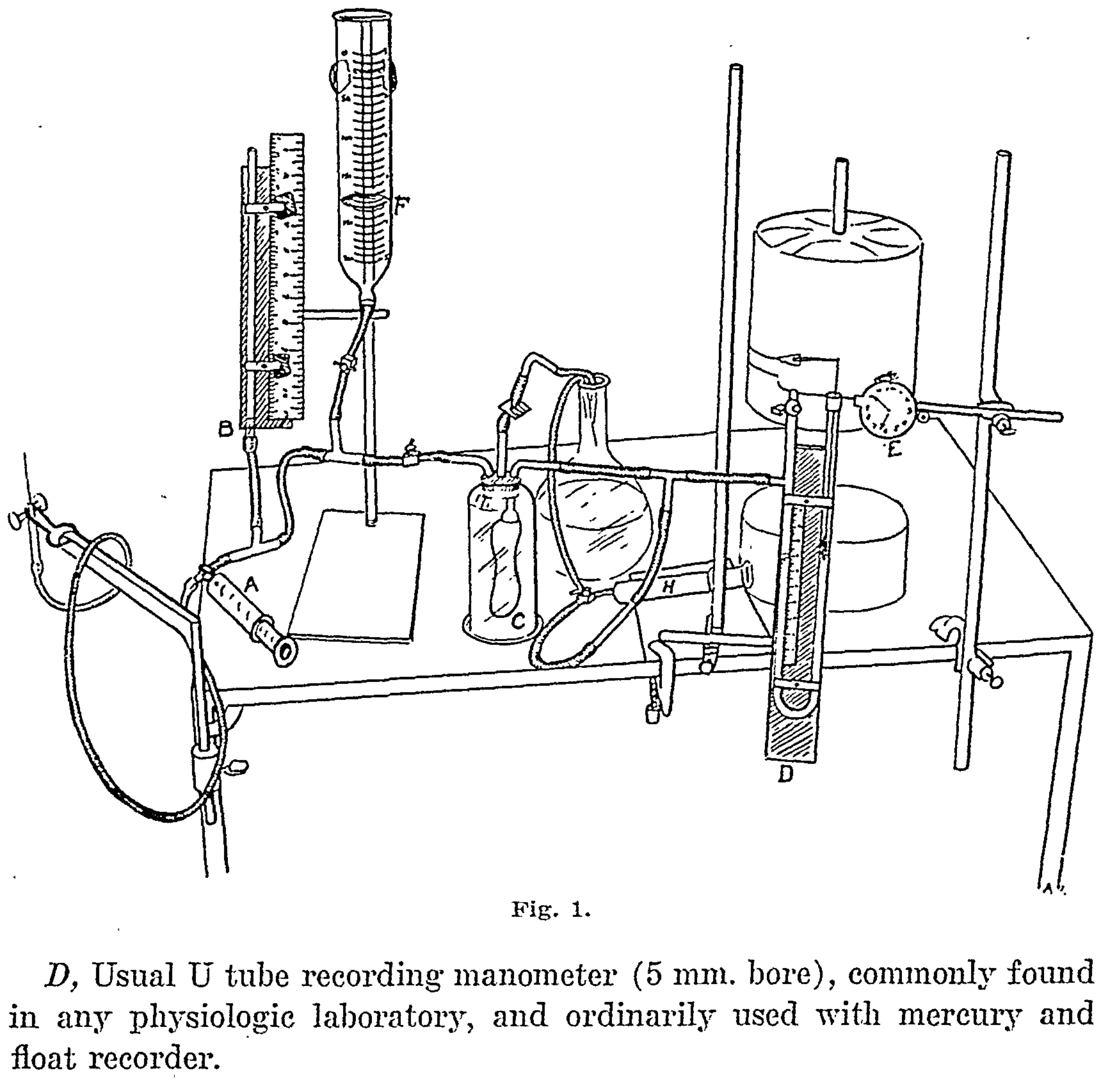

Fig. 1.

D, Usual U tube recording manometer (5 mm. bore), commonly found in any physiologic laboratory, and ordinarily used with mercury and float recorder.

Because of surface tension, a light cork float cannot be used on water, for it sinks or sticks when the water level goes up or down. This can be obviated by filling the manometer with a heavier liquid (trichlorethylene or carbon tetrachloride) which is not readily water soluble, add-

ing a drop or two of a commercial detergent solution (Duponol*) just where the light cork float meets the trichlorethylene. The cork float (7 mm. long and about 4 mm. in diameter), with a light straw guide and writing point, now moves up and down lightly and accurately on the drum. The right amount of Duponol solution around the cork float is important to prevent lag as the cork rises and falls, and just enough is used to extend the exact length of the cork as it rests on the heavier fluid in the manometer. The use of a commercial detergent to diminish surface tension about the cork float is the key to the accuracy of the recording manometer.

Liquids of varying specific gravity may be used, depending on how much excursion of the manometer is desired. The heavier ones are, of course, required for wide ranges involving high venous pressures, so that the writing point does not go off the drum. Heavier liquids, such as methylene bromide, increase the lag slightly. Water also can be used, but Duponol soon diffuses into water, and hence the necessity of using heavier, relatively water insoluble liquids in the manometer. We have found that the ones shown in Table I are suitable.

TABLE I

NAME	SPECIFIC GRAVITY	EXCURSION IN MM. ON DRUM PER 20 MM. WATER STANDARDIZATION
Trichlorethylene	1.455	10.5
Carbon tetrachloride	1.595	9.3
Methylene bromide	2.495	5.25

Additional heavy liquids that are relatively water insoluble are S-tetrabromethane, specific gravity 2.965, and methylene iodide, specific gravity 3.285.

E, F, and *H*, A time watch (*E*), base line lever, and respiration recording lever may be added. As the apparatus is set up here, the reservoir (*F*) is filled with 2 per cent, sterile citrate solution. This is used to fill the sterile half of the system, but is not used after the experiment is started, for clotting is prevented by the use of syringe (*A*). The nonsterile side of the system is filled with syringe (*H*).

The point of reference is obtained, as previously suggested,[5] by leveling the zero point of manometer *B* with a point 10 cm. above the level of the back of the horizontal patient. Surface tension where the needle is in the vein may prevent obtaining a correct zero level; this may be overcome by allowing the needle to overflow into the container of sterile citrate at zero level.

We have made about fifty observations on patients with this method, and have obtained continuous graphic records of venous pressure over periods of twenty to forty-five minutes. One such record (Fig. 2) is shown, with calibration. Also, simultaneous sight readings and values

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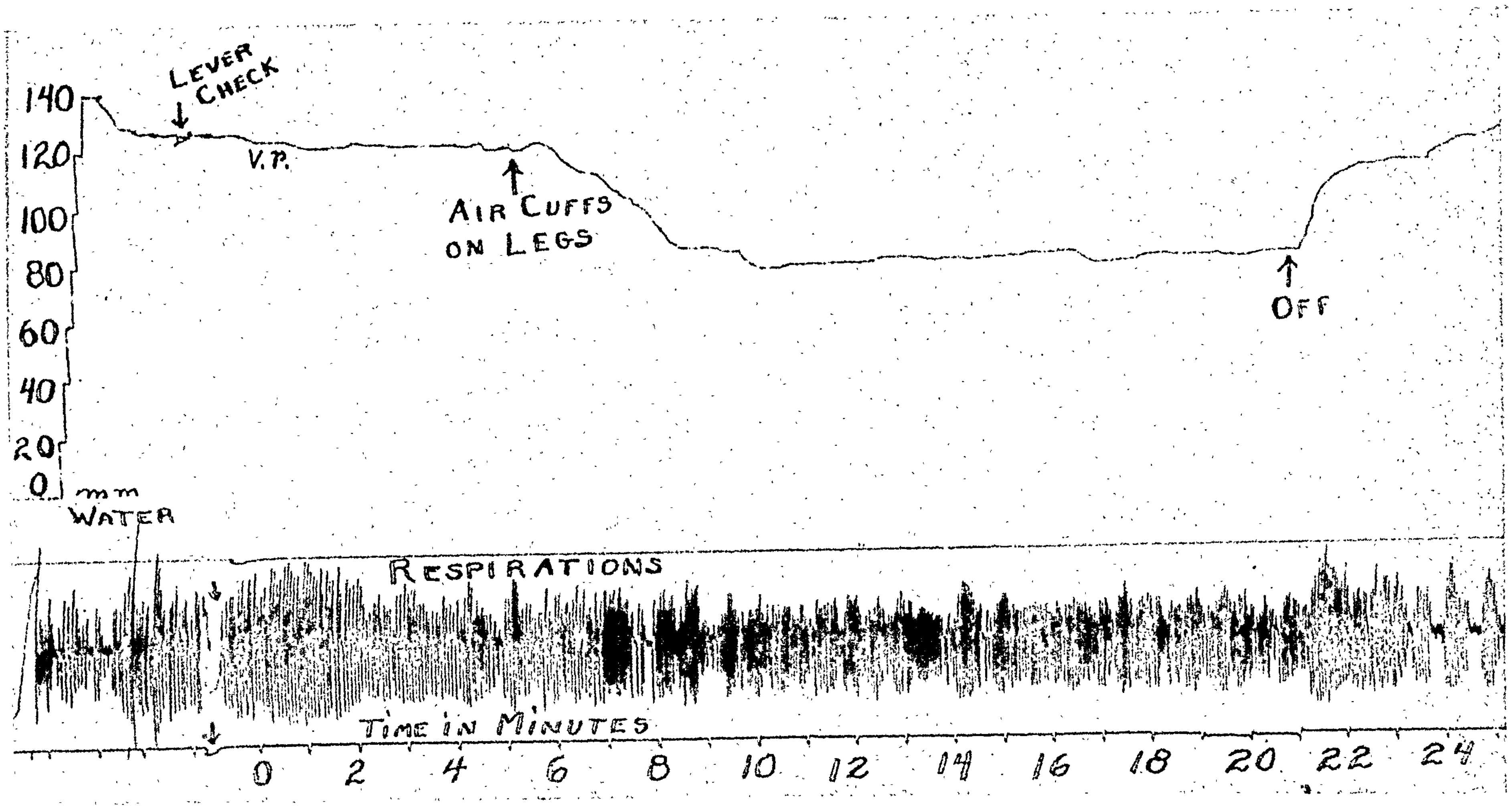

Fig. 2.—Venous pressure *(V.P.)* recorded twenty-seven minutes. Blood pressure cuffs on thighs, inflated to 80 mm. Hg, bring about fall of venous pressure as measured in vein of left arm. Tracing is a positive print from smoked paper used as a negative.

Table II

	Manometer B sight readings mm. H_2O (citrate)	Manometer D values recorded on drum mm. H_2O (citrate)
0 min.	126	125
1	123	123
2	121	121
3		121
4		121
5		121
6		121
7	110	110
8	97	99
9	84	83
10	76	80
11	78	77
12	77	77
13	79	79
14	79	78
15	80	79
16	81	80
17	76	77
18	79	77
19	78	78
20	78	77
21	78	79
22	104	102
23	110	109
24		110
25		117
26	123	122
27	126	124
28	128	127
29	131	130
30	128	128
31	135	133
32	134	133

from graphic curves are shown (Table II) to illustrate the accuracy of the recording manometer. Slight discrepancies may be caused, in part, by the failure of a single observer to catch sight readings exactly, by a slight mechanical error in synchronizing the level and time marker, and by slight frictional lag. If the manometer is set up correctly, calibration up and down scale should be even and without appreciable error. The manometer records the venous pressure changes which occur during Cheyne-Stokes breathing, forced dyspnea, the Valsalva phenomenon, excitement, slight muscular movements, venous pooling, as illustrated in Fig. 2, and under other conditions. It appears to be a simple, mobile, inexpensive method for recording venous pressures.

It is of added interest that ordinary smoked drum records may be used as negatives, and printed on photographic paper. Although smoked cellophane provides a smoother surface and therefore possibly diminishes friction, we have not found it necessary for photographic reproduction, as previously suggested.[8]

This modification of the method of Moritz and von Tabora[7] permits accurate, graphic registration of venous pressure in man.

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STUDIES ON THE PRODUCTION AND MAINTENANCE OF EXPERIMENTAL AURICULAR FIBRILLATION

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FROM the time auricular fibrillation was first described in man[1, 2] and was shown to be a common condition,[3] observers have attempted to gain more insight into its causes. Earlier work[4, 5] demonstrated that irritation of the auricles by faradizing currents often produced transient auricular fibrillation in the experimental animal. Other workers[6, 7] noted that, during vagus stimulation, the atria were often more likely to fibrillate when stimulated by faradic currents, and that fibrillation frequently occurred with vagus stimulation alone. Recently, acetyl-beta-methylcholine (mecholyl) has been used to produce the effect of vagus (parasympathetic) stimulation. Nahum and Hoff[8] found that placing pledgets of mecholyl upon the auricular surfaces of the dog heart often produced fibrillation. Noth, Essex, and Barnes[9] and Iglauer and his co-workers[10] noted transient atrial fibrillation in dogs after the intravenous administration of mecholyl. Similar phenomena have been observed in human subjects. Batro and Lanari[11] noticed the occurrence of atrial fibrillation in a patient after the intracarotid injection of acetylcholine, and Dameshek, et al.,[12] observed this arrhythmia after the administration of prostigmine and mecholyl. These experiments emphasize the probable importance of vagal stimulation in the production of auricular fibrillation.

The experiments of Nahum and Hoff[13] are of particular interest. These workers were able to induce transient auricular fibrillation in thyrotoxic patients by the administration of acetyl-beta-methylcholine. They postulated that the application of an irritative factor to the auricles ("E" factor), upon which vagal stimulation is superimposed, is necessary to cause fibrillation of the auricles. They further suggested that, in mitral stenosis, the condition of auricular distention may operate as the "E" factor, added to which vagal stimulation may precipitate the disorder. Auricular distention as an influence in the establishment of atrial fibrillation in mitral stenosis had been previously suggested.[14-16, 21]

Our interest in conditions which might induce and maintain auricular fibrillation was aroused while we were performing experiments for another purpose. In perfusing the coronary arteries of the heart-lung preparation with anoxemic blood, we repeatedly noted the spontaneous occurrence of auricular fibrillation. As these hearts were in

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Received for publication March 3, 1943.

good condition, and the only altered factor was the perfusing of anoxemic blood, it seemed possible that oxygen lack might favor the development of the arrhythmia. Such a possibility has been suggested by a number of independent studies. Porter,[17] many years ago, observed the disappearance of atrial fibrillation after perfusing the coronary vessels with oxygenated blood. Lewis[18] found that paroxysmal auricular tachycardia frequently followed ligation of the right coronary artery of the dog heart; during the course of the tachycardia, atrial fibrillation often occurred. De Boer[19] noted atrial fibrillation after ligation of the coronary vessels, or when the heart was in a "poor metabolic state," and Resnik[34] found that auricular anoxemia may predispose the auricles to fibrillation. Géraudel[20] spoke of tachycardias and arrhythmias caused by interference with the blood supply of the myocardium. Master and his associates[21] suggested that auricular fibrillation after acute coronary thrombosis depended upon altered metabolism, anoxemia, and impaired nutrition of the myocardium.

In order to study further the possible role of auricular anoxemia in the production of atrial fibrillation, the following experiments were performed.

METHODS AND RESULTS

FIG. 1

1. *Effect of Anoxemia and Mecholyl in Producing Atrial Fibrillation in the Normally Beating Heart.*—Experiments were performed on nineteen dogs, each of which weighed approximately 15 kilograms. Under nembutal anesthesia, the thorax was opened by cleaving the sternum; respiration was maintained by means of a pump attached to an intratracheal cannula. A glass cannula was introduced into a femoral vein for the administration of mecholyl. An electrocardiograph was attached by embedding German silver electrodes in the shoulder and left leg muscles. In order to produce the effect of moderate vagus stimulation, doses of mecholyl of 0.12, 0.14, 0.16, or 0.18 mg. were arbitrarily chosen, and given individually. The smallest dose which produced transient cardiac arrest (5 to 10 seconds) or marked slowing of the sinus rhythm was selected as the control dose. Usually, 0.12 mg. sufficed to produce this effect.

When Lead II had been obtained and the effect of the control dose of mecholyl had been observed, the respiratory pump was stopped. Marked anoxemia was permitted to develop, as judged by the gasping respiration of the animal and the deepening hue of the blood in visible arteries. During anoxemia, the control dose of mecholyl was administered again, while a continuous electrocardiographic tracing was made. Care was taken to avoid accidental mechanical stimulation of the auricles. In all of the animals during anoxemia, mecholyl induced cardiac arrest for 10 to 25 seconds, together with marked dilation of both auricles and

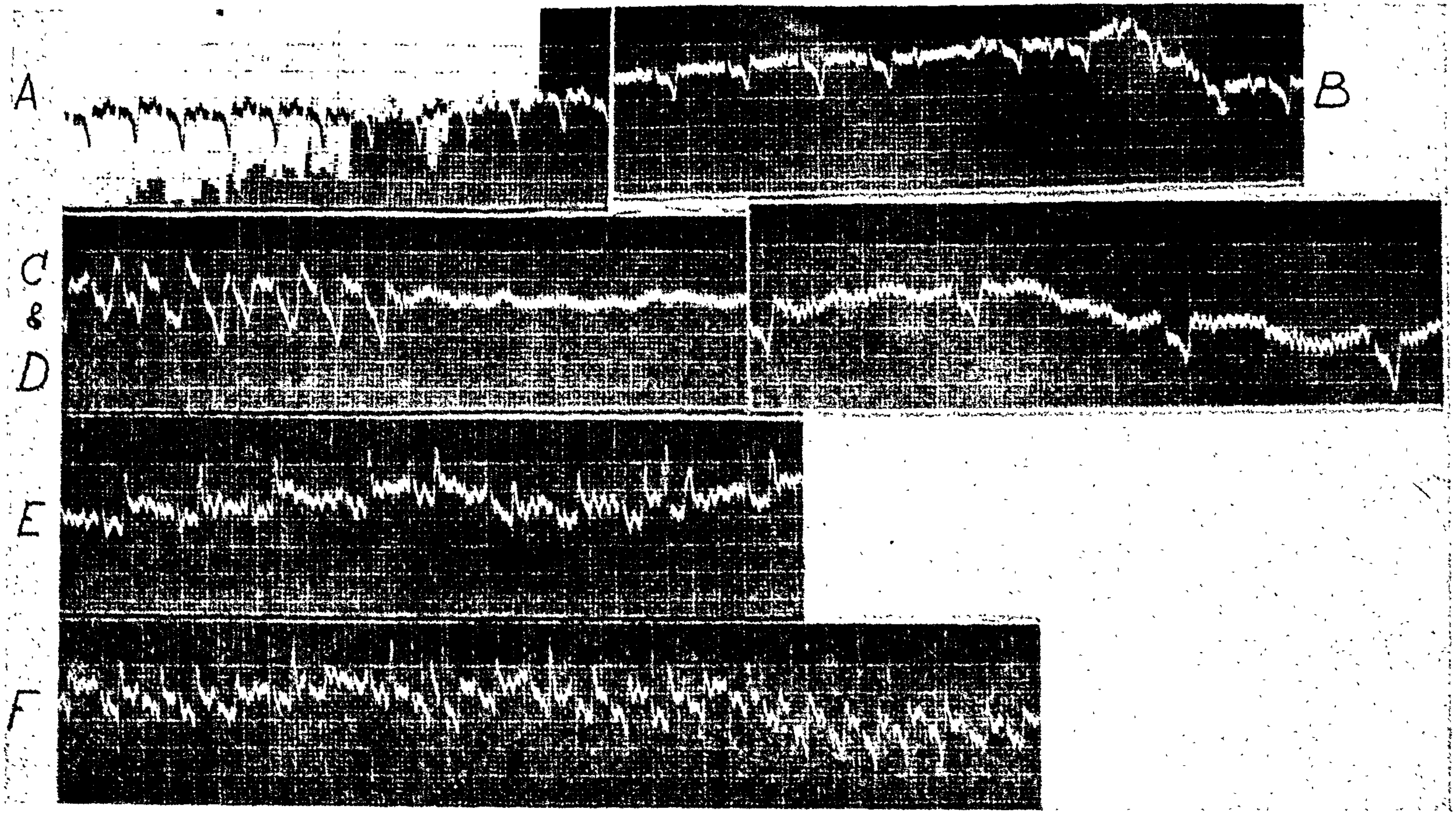

Fig. 1.—Electrocardiograms (Lead II) taken during the course of Experiment 1. *A* is the control curve. *B* shows the definite slowing of sinus rhythm after the intravenous administration of 0.12 mg. of mecholyl. During asphyxia (*C*), the marked, gross deflections of the string resulted from the gasping respiration of the dog, and the readministration of 0.12 mg. of mecholyl (*C*) then produced cardiac arrest (30 seconds), followed by spontaneous auricular fibrillation (*D*) with complete heart block. Auricular fibrillation persisted during anoxemia. Upon re-aeration the *f* waves became more pronounced (curve *E*). In curve *F* is seen the sudden disappearance of flutter-fibrillation and the establishment of sinus mechanism.

ventricles, whereas, in the control observations, the same amount of the drug produced sinus slowing or only transient arrest. The asystole was followed by idioventricular rhythm. In ten of the nineteen animals auricular fibrillation developed spontaneously. It usually appeared soon after vagal escape, or at the end of auriculoventricular standstill. Fibrillary motions were first manifest in the auricular appendages, and were always "fine" in character. As the effect of the mecholyl passed off, "fine" auricular fibrillation persisted; with the disappearance of auriculoventricular dissociation, the ventricular contractions became rapid and absolutely irregular.

The resumption of respiration was followed by abolition of auricular fibrillation and the re-establishment of normal cardiac mechanism. In two or three minutes after aeration was begun, the fibrillary contractions (and electrocardiographic *f* waves) became more coarse, transient auricular flutter or flutter-fibrillation ensued (persisting, usually, 60 to 120 seconds), and normal sinus rhythm was then regained. However, if, after anoxemia and auricular fibrillation had been established, the respirator was adjusted in such a way as to maintain the blood at an anoxemic level, auricular fibrillation persisted. In this way auricular fibrillation was frequently maintained for as long as thirty minutes. It was seldom possible to perpetuate anoxemia for a longer period because of the occurrence of pulmonary edema.

In nine of the animals, auricular fibrillation did not occur spontaneously, even when the experiment was repeated with the highest (0.18 mg.) test dose of mecholyl. However, under the influence of both anoxemia and mecholyl, gentle mechanical stimulation of the auricles by light stroking with a feather immediately precipitated auricular fibrillation, whereas, in the absence of anoxemia, strong mechanical stimuli must be applied to the auricles in order to induce fibrillation. The response of auricular fibrillation in these hearts to persistent anoxemia and re-aeration was the same as in the foregoing group.

2. *Elimination of the Factor of Auricular Distension.*—Nahum and Hoff[13] and others [14-16, 21] have suggested that distension of the auricles in mitral stenosis may be important in initiating atrial fibrillation. In the foregoing experiments, during the cardiac arrest produced by the administration of mecholyl, there was obvious, marked dilatation and distension of the cardiac chambers. As the factor of distension could not be eliminated in these observations, another series of experiments was undertaken in an attempt to avoid increased intra-auricular tension.

FIG. 2

Four experiments were performed on four dogs. Starling heart-lung preparations were set up, and the hearts were adjusted to work under a pressure of 90 mm. Hg and with an output commensurate with the size of the organ. A perfusion flask was arranged so that blood, un-

der any desired pressure, could be perfused into the aorta and against the aortic valves; the blood passed thence into the coronary arteries. Electrocardiograms were taken before and during the experimental procedures. While the heart-lung preparation was beating normally, 0.12 mg. of mecholyl (or amounts of 0.14, 0.16, or 0.18 mg., as desired) was administered through the cannula in the vena cava. The quantity of

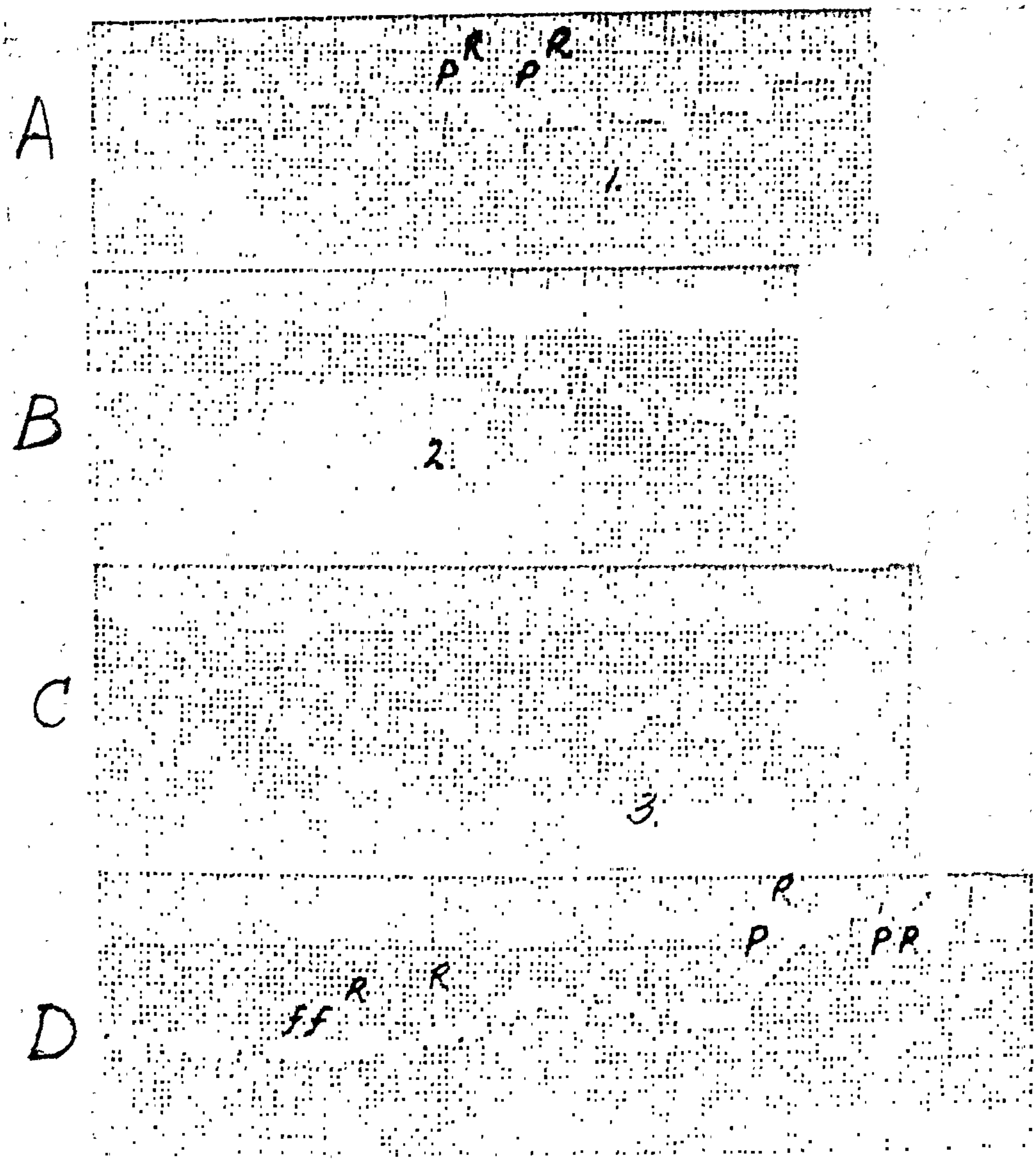

Fig. 2.—Electrocardiograms (Lead II) recorded during perfusion of the coronary vessels in Experiment 2. *A* is the control curve. *B* is the curve taken during the perfusion of venous blood into the coronary arteries (with the heart beating empty). After the administration of 0.12 mg. of mecholyl, auricular fibrillation occurred (curve *C*), and, with perfusion of oxygenated blood (curve *D*), coarse fibrillation ensued, followed by the return of normal sinus rhythm.

drug which produced an evanescent arrest of the heart, or marked slowing of the sinus rhythm, was again chosen as the control dose. The venous inflow to the heart was then shut off, entirely eliminating flow through the heart. In this state, the auricles and ventricles were col-

lapsed. Venous blood (anoxic) was then perfused into the aorta and coronary vessels under a pressure of 90 mm. Hg, and the control dose of mecholyl was reinjected into the perfusing blood. In all four experiments, there immediately followed a period of cardiac arrest, 10 to 20 seconds in duration, followed by idioventricular rhythm of 30 to 60 seconds' duration. Spontaneous atrial fibrillation occurred in each heart. Again, fibrillation of the auricles persisted during the time anoxemic blood was used in perfusion. When oxygenated blood was again forced into the coronary arteries, coarser fibrillary movements promptly occurred, followed by transient flutter-fibrillation and finally normal rhythm.

No attempt was made to maintain auricular fibrillation for long periods of time, as it would have required large amounts of anoxemic blood in constant circulation. Auricular fibrillation was permitted to continue for several minutes in each experiment.

3. *Production of Auricular Fibrillation in Hearts With Acute Experimental "Mitral Stenosis."*—The question whether extreme distension of the auricles influences the normal auricular mechanism was investigated by producing acute "mitral stenosis" in five dogs. In two experiments heart-lung preparations were used; in one experiment, the heart was exposed and the general circulation kept intact; chlorazol fast pink and heparin were given to prevent clotting during subsequent procedures. In all three of these experiments small incisions were made in the left auricular appendages. A brass tube, 3 mm. in diameter, to the end of which a small balloon was affixed, was passed through the auricle into the left ventricular cavity and tied in place by a ligature placed around the aperture.[22] Careful partial inflation of the balloon encroached upon the volume of the ventricular cavity, producing a retrograde increase of pressure in the left auricle, pulmonary vessels, and right cardiac chambers. The balloon was sufficiently inflated so that left ventricular output was curtailed by about 10 per cent. Marked distension of both auricles and the right ventricle resulted. When the balloon was in place and inflated, 0.12 or 0.14 mg. of mecholyl was injected into the vena cava or femoral cannula, while continuous electrocardiographic tracings (Lead II) were taken. In the three experiments, auricular fibrillation developed spontaneously and persisted as long as the inflated balloon (and, therefore, auricular distension) was retained. It was not possible to maintain auricular distension for more than five minutes because of the rapid development of pulmonary edema. Release of the balloon and the re-establishment of normal intracardiac pressures were followed by auricular flutter and restoration of normal mechanism, as in the foregoing experiments.

In two additional experiments, using dogs with hearts exposed and circulation intact, an attempt was made to produce acute mitral stenosis by the method of Katz and Siegel.[23] In this method, sutures are drawn

through the myocardium and under the leaves of the mitral valve in such a way that tension on the sutures raises the mitral cusps to produce a "stenosis." However, in each of these experiments, auricular fibrillation occurred spontaneously as the sutures were being placed, and before auricular distension could be produced. It was thought that direct injury to the atria produced the fibrillation.

DISCUSSION

The experimental data presented would indicate that anoxemia of the auricles, together with vagal stimulation, may result in the spontaneous development of atrial fibrillation, with or without auricular distension. In the interpretation of these observations, several factors must be considered.

Nahum and Hoff[13] have pointed out that the degree of vagus excitation may be of considerable importance in the establishment of auricular fibrillation. The experiments of Lewis, Drury, and Bulger[24] and of Andrus and Carter[25] have shown that stimulation of the vagus conspicuously decreases the refractory period of the auricle, and that the application of a stimulus to the auricle shortly after the end of the refractory period under vagal stimulation resulted in the occurrence of auricular fibrillation. It seems possible, therefore, that, because of shortening of the refractory period, stimuli may fall upon auricular muscle which is excitable, but in which conductivity has not returned to normal. The muscle is thus receptive to re-entrant rhythms.[25]

The mechanism by which anoxemia of auricular muscle facilitates the induction of atrial fibrillation on stimulation of the vagus is not entirely clear. Wiggers[26] notes that, in ordinary heart muscle, anoxemia may increase the irritability of foci in the ventricle, or may cause delayed conduction and regional blocks, permitting the re-entry of excitation waves into normal muscle. These changes may give rise to fibrillation. It seems reasonable that similar conditions may occur in anoxemic auricular muscle. Cushing and his co-workers[27] found that, in producing auricular infarcts in the experimental animal, abnormalities in auricular mechanism frequently occurred, such as premature systoles, wandering pacemakers, tachycardias, and other disturbances, indicating greatly increased irritability of the muscle. On the other hand, anoxemia of auricular muscle appears to have very little effect on the refractory period of the muscle.[28] Therefore, it seems possible that an auricle which has been rendered irritable by anoxemia may be precipitated into fibrillation by the additional factors of shortened refractory period and lessened conductivity produced by vagal stimulation of sufficient degree.

Heymans and his associates[29] and Richard[30] have shown that the effect of vagal stimulation on the heart is greatly enhanced by anoxemia. In our experiments, the effect of acetyl-beta-methylcholine on cardiac inhibition was strikingly increased when the heart was deprived of oxy-

gen. Intravenous injections of 0.12 mg. of the drug produced arrest of cardiac contraction and periods of vagal escape of much longer duration in the presence of anoxemia than in its absence. It seems probable, therefore, that anoxemia and vagal stimulation act synergistically in the production of atrial fibrillation.

The clinical implications embodied in these experiments are possibly of interest. The common occurrence of auricular fibrillation in coronary artery disease, myocardial infarction, and congestive heart failure is well known. From the clinical standpoint, one might wonder whether, in heart disease which is attended by reduced coronary artery flow and anoxemia of the myocardium, normal vagal stimuli might not be amplified in their effects upon the heart, leading, in some cases, to the establishment of auricular fibrillation. Indeed, Weiss and Baker[31] found that, in patients with coronary disease, carotid sinus stimulation tended to produce marked temporary slowing of the heart. Sigler[32] noted high degrees of cardio-inhibitory response to carotid sinus stimulation in cases of coronary insufficiency.

Distension of the auricles in mitral stenosis has seemed likely as a factor in the causation of fibrillation of the atria. In the dog heart, auricular distension caused by obstructing the passage of blood through the left ventricle, together with an acetylcholine effect, resulted in the spontaneous development of fibrillation. However, when auricular distension was eliminated by perfusing the coronary vessels while the heart was beating empty, auricular fibrillation was again spontaneously produced when the muscle was perfused with anoxic blood under vagal stimulation. From the clinical standpoint, one would feel that the factors of auricular distension and anoxemia are inseparable. Kountz and Smith[33] suggested that distension of the ventricular wall might so stretch the intramural coronary radicles that marked reduction of the flow of blood would result. Distension of the thin auricular walls, producing marked attenuation of the intramural vessels, and, consequently, anoxemia of the muscle, would seem to be a possible factor in the production of auricular fibrillation.

Cushing and his co-workers[27] produced auricular infarction in the hearts of dogs by ligating the auricular arteries. They noted various changes in auricular mechanism, but auricular flutter occurred in only one of their experiments, and auricular fibrillation was not noted. Therefore, their results might at first glance appear to be at variance with ours. One possible explanation for this difference may be that anoxemia of the auricular muscle, as a whole, may be required before conditions necessary to the production of auricular fibrillation develop. In mitral stenosis, congestive heart failure, and in some cases of myocardial infarction (in which this arrhythmia is common), anoxemia of all of the auricular muscle conceivably occurs, possibly fostering the onset of the arrhythmia.

SUMMARY

The relationship of anoxemia of the auricles and vagal stimulation (mecholyl effect) was investigated in the hearts of dogs. In the normally beating heart it was found that: (1) anoxemia apparently renders the heart more sensitive to the action of mecholyl; (2) auricular fibrillation frequently occurs spontaneously, or is easily induced by minute, mechanical, auricular stimuli after small doses of mecholyl during anoxemia; (3) reoxygenation of the blood results in the restoration of normal cardiac mechanism. In another series of experiments, the factor of auricular distension was eliminated by perfusing the coronary vessels of the heart while the heart was beating empty; the administration of mecholyl during perfusion with anoxic blood produced auricular fibrillation. Mecholyl also produced auricular fibrillation in hearts with acute, experimental "mitral stenosis."

The possible mechanisms by which auricular anoxemia, together with the action of mecholyl, may precipitate atrial fibrillation are discussed, and the clinical aspects considered.

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THE EFFECT OF THYROID EXTRACT, ADRENALIN, AND A COMBINATION OF THESE ON THE HEARTS OF INTACT AND THYROIDECTOMIZED RABBITS

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THE exact mechanism whereby thyroid extract and adrenalin affect the heart is still not clear. Thyroid extract causes an increase in cardiac output by increasing the heart rate and stroke volume. Adrenalin causes a rise in heart rate and blood pressure, and also has an effect on the heart by a synergistic action with the thyroid gland. The ultimate cause, however, of the cardiac enlargement and myocardial fibrosis which follow the administration of thyroid extract and adrenalin to animals is far from clear.

A person with myxedema or anyone after complete thyroidectomy[1] is usually more sensitive to thyroid extract than normal. In this work an attempt was made to answer the question whether the effect of thyroid extract was greater on the hearts of thyroidectomized rabbits than on those of intact rabbits. Similarly, the effect of adrenalin on similar groups of animals was studied. An attempt was also made to ascertain whether adrenalin augments the effect of thyroid extract.

REVIEW OF LITERATURE

Hoskins,[2] Cameron and Carmichael,[3] and Hashimoto[4] reported cardiac hypertrophy in rats which were fed thyroid extract. Hashimoto also noted that the effect (grossly, dilatation, and, microscopically, swelling of muscle fibers and increased interstitial fibrosis) depended upon the duration and dosage of the thyroid extract. Goodpasture[5] found cardiac hypertrophy in rabbits which had been given thyroid or thyroxin. After two to three weeks of treatment he observed myocardial and perivascular necrosis, fibrosis of papillary muscles, and an increased susceptibility to myocardial injury from chloroform. Simonds and Brandes[6] observed generalized cardiac hypertrophy, especially of the left ventricle, in dogs which had been fed desiccated thyroid extract.

Smith and MacKay[7] observed a linear relation between the weight of the heart and the basal metabolism in rats that were fed thyroid extract. They noted a direct relationship between the work of the heart and the weight of the heart. The isolated hearts and auricles of thyroid-treated animals were shown by Lewis and MacEachern[8] to continue to beat at a faster rate than normal. In frizzle fowl Boas and

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Received for publication March 12, 1942.
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Landauer[9] demonstrated left ventricular hypertrophy and an increase in the ratio of ventricular weight to body weight. They attributed the increased work of the heart to permanent tachycardia caused by a persistently elevated metabolism.

Hypertrophy of the heart in animals following injections of adrenalin was reported by Stewart[10]; the degree of hypertrophy was determined by the amount of adrenalin injected. He believed that adrenalin produced a metabolic disturbance due to a direct toxic action on the muscle fiber, with histologic changes similar to those which follow diphtheria. The hypertrophy of the heart was in proportion to the myocarditis, with increases in weight up to 42 per cent in those with myocardial lesions and up to 26 per cent in those with microscopic changes. He believed that the early stage of cardiac hypertrophy is caused, in part, by an increased water content, and that, after the third week of adrenalin injections, the edema disappears.

Kuriyama[11] demonstrated no increase in weight or in epinephrine content of the adrenals of thyroid-fed rats, presuming that adrenalin is transferred to the circulation. He does, however, state that the action of adrenalin on the frog or rabbit heart is augmented by additions of thyroid extract. He mentions the fact that the plasma of rats which had been fed thyroid and of patients with Graves' disease accelerates the vasoconstrictor influence of epinephrine. According to Schermann,[12] thyroidectomy decreases the response of the isolated heart to adrenalin. This decreased response is due to a lack of thyroid effect on the nerve-muscle cell-endings of the heart.

Herring[13] is of the opinion that, with thyroid feeding, the activity of the animal's own thyroid adds another factor to the degree of response. He thinks that the animal's own thyroid gland is restrained in development by prolonged thyroid feeding. He found hypertrophy of the heart, kidneys, pancreas, liver, and suprarenals as a result of thyroid feeding. In the suprarenals the increase in medullary substance was more than balanced by greater hypertrophy of the cortex.

The synergism between the adrenal and the thyroid gland is well known. Asher and Flack[14] demonstrated that the thyroid sensitizes the sympathetic endings to the action of adrenin. Oswald[15] observed that, after intravenous injections of iodothyroglobulin, adrenin causes a rise in pressure which is higher and longer in duration than before. Levy[16] observed a prompt liberation of thyroid after sympathetic stimulation. According to Zwemer,[17] absence of the thyroid gland tends to delay the onset of symptoms of adrenal insufficiency.

Marine and Baumann[18] showed that the suprarenal cortex normally exerts a regulatory and inhibitory control over thyroid activity, which, when lost, automatically leads to increased activity, with heightened heat production. Thyroidectomy prevents or diminishes the rise in respiratory exchange which usually follows sublethal injury to the

TABLE I

NO. OF ANIMAL AND SEX	NO. OF DAYS OF EXPERIMENT	AMT. OF MEDICATION*	WEIGHT AT END, GAIN, LOSS	HEART WT.	HEART WT./ BODY WT. RATIO	NO. OF ANIMAL AND SEX	NO. OF DAYS OF EXPERIMENT	AMT. OF MEDICATION*	WEIGHT AT END, GAIN, LOSS	HEART WT.	HEART WT./ BODY WT. RATIO	NO. OF ANIMAL AND SEX	NO. OF DAYS OF EXPERIMENT	AMT. OF MEDICATION*	WEIGHT AT END, GAIN, LOSS	HEART WT.	HEART WT./ BODY WT. RATIO
Group I—Thyroidectomized Animals																	
Control Animals						*Adrenalin Group*						*Adrenalin-Thyroid Group*					
351 M	26	0	2231 +504	3.8	0.174	356 M	26	0 14.2	1960 +778	3.1	0.158	360 M	20	1.5 10.2	1447 -402	4.9	0.338
350 M	30	0	2534 +480	3.3	0.154	357 M	29	0 16.6	1685 - 98	3.5	0.207	362 M	29	2.3 16.6	1235 -425	4.9	0.397
353 M	33	0	2225 +470	3.9	0.175	358 M	33	0 19.8	1858 + 37	3.1	0.166	359 M	31	2.5 18.2	1460 -240	6.5	0.445
349 M	37	0	2031 +352	4.4	0.216	355 M	35	0 21.4	2068 +203	3.8	0.184	363 M	35	2.9 21.4	1659 + 37	6.7	0.404
352 M	40	0	2914 +1147	5.7	0.195	354 F	37	0 23.0	2208 +492	3.2	0.149	361 M	36	3.0 22.2	2072 +213	5.7	0.275
Group II—Intact Animals																	
						Adrenalin Group						*Adrenalin-Thyroid Group*					
						383 M	33	0 10.9	2115 -285	4.9	0.232	377 M	23	4.7 11.1	1638 -405	5.2	0.317
						380 M	40	0 13.7	2388 +160	4.9	0.252	379 M	38	2.6 6.6	1424 -616	5.5	0.386
						382 M	57	0 20.5	2682 +640	6.8	0.254	374 M	57	6.8 20.5	1985 - 90	6.5	0.327
						381 M	64	0 23.3	2168 +146	5.1	0.235	378 M	64	7.9 23.3	2150 + 62	6.8	0.326
						385 M	80	0 31.9	2986 +957	6.6	0.221	375 M	81	9.5 34.9	2238 - 42	6.6	0.295
						384 M	95	0 40.9	3855 +1657	8.4	0.218	376 M	95	10.9 40.9	3255 +1197	9.2	0.283

Group III—Thyroid-Adrenalin Treated Animals

Thyroidectomized Group						*Intact Group*					
386 F	18	1.8	1134	4.1	0.361	396 M	18	1.8	1085	4.0	0.369
		5.4	- 44					5.1	-546		
391 M	25	2.4	1850	5.2	0.281	397 M	25	2.4	1701	5.4	0.317
		7.7	+ 5					7.7	-186		
388 F	29	2.8	1542	4.8	0.311	393 F	29	2.8	1574	4.9	0.311
		10.0	+142					9.3	+193		
390 M	39	4.2	1446	4.9	0.339	392 F	39	4.2	1040	4.6	0.442
		14.6	+192					14.6	-152		
389 M	48	5.7	2342	6.7	0.290	395 M	46	5.4	2023	7.1	0.351
		19.1	+288					17.8	+ 89		
387 F	64	9.6	1615	7.0	0.433	394 F	64	9.6	1300	6.1	0.469
		27.1	-315					27.1	-665		

Group IV

Thyroidectomized Animals Given Thyroid Extract						*Intact Animals Given Thyroid Extract*						*Intact Animals Gives Thyroid Extract and Adrenalin*					
7 M	90	7.5	3454	6.3	0.182	12 M	7	0.2	1450	5.8	0.400	16 M	14	0.4	1430	4.0	0.280
			+826						-565					3.9	-801		
9 M	79	7.1	2501	7.2	0.287	13 M	78	7.1	2621	7.5	0.286	18 M	49	5.8	2205	6.9	0.313
			- 41						+269					14.4	-188		
10 M	77	7.1	2404	6.5	0.270	14 M	77	7.1	2655	7.6	0.286	19 F	82	7.1	2404	5.1	0.260
			+ 27						+398					24.3	-436		
11 M	19	1.0	2227	7.2	0.323	15 M	94	7.5	3290	6.2	0.207	20 F	85	7.5	2905	6.8	0.234
			-239						+482					25.2	- 55		

*Under the heading "Amount of Medication," upper figure denotes total dose of thyroid extract in grams, and lower figure, total dose of adrenalin in milligrams.

suprarenal glands. Seely and Cutler[19] found that thyroidectomized dogs showed a great loss of sensitivity of sympathectomized vessels to adrenalin. They also found that, when patients were deprived of thyroid secretion, injections of adrenalin produced less vasoconstriction.

In an attempt to ascertain the effects of adrenalin alone, and of a combination of thyroid extract and adrenalin upon the hearts of thyroidectomized and normal rabbits, four groups of rabbits were studied. The first group consisted of fifteen thyroidectomized rabbits. Of these, five served as controls, five were given subcutaneous injections of 0.3 to 0.4 mg. of adrenalin in aqueous solution, and five others received the same dose of adrenalin, plus 100 mg. of desiccated thyroid extract by mouth daily. The dose of the drugs was decreased if weight loss was too great or the animals appeared ill, and increased if the effect on the heart, as observed at necropsy, on others was not marked.

To ascertain whether thyroidectomy augmented the effect of thyroid extract and adrenalin, another group of twelve animals with intact thyroids were treated in a similar way, except that adrenalin in oil (0.3 to 0.4 mg. daily) was substituted for adrenalin in aqueous solution in the hope of producing a more prolonged effect instead of the sudden and transitory, though marked, effect of the aqueous adrenalin solution. Half the number were given adrenalin alone, and the other half were given thyroid in addition to adrenalin. The dose of thyroid extract and adrenalin was increased or decreased as the hearts were observed after different experimental periods. At the end of the experiment the animals were receiving 0.6 mg. of adrenalin in oil daily.

To ascertain the effect of thyroidectomy, a third group of twelve animals, half of which were thyroidectomized and the other half intact, were given the same doses of thyroid (200 to 300 mg. of desiccated thyroid by mouth) and adrenalin in oil (0.3 to 0.5 mg. subcutaneously) daily. The experiments lasted from eighteen to sixty-four days. In this group, thyroidectomy did not appear to increase the changes in the heart produced by thyroid extract and adrenalin.

A fourth group was studied because it was felt desirable to ascertain the effect of thyroid extract on the intact and the thyroidectomized animal, i.e., to see whether the thyroidectomized rabbit was more sensitive to thyroid than the intact one. This group was composed of twelve animals, divided into three sets of four each. Four intact and four thyroidectomized rabbits were given thyroid extract, and four intact animals were given thyroid extract and adrenalin.

In addition, the clinical manifestations and necropsy observations in three goitrous rabbits which pursued a fatal course of hyperthyroidism after the administration of small doses of iodine are discussed.

RESULTS

Group 1.—Thyroidectomized rabbits.

Heart: a. Control Section.—The survival period was up to one month. Minor changes occur fairly frequently in the rabbit's myocardium. These were found in the control group, and consisted of areas of hyaline degeneration with vacuoles in some of the fibers. Foci also occurred in which the cytoplasm was dense and deeply red, with shrunken, irregular, pyknotic nuclei. These foci occurred in both the right and

left ventricles. The changes tended to be more marked in the left than in the right. The vessels were normal. Areas of marked loss of cytoplasm, with fraying out of muscle cells in places at the periphery, were observed. The changes were more marked in some than in others.

b. In the adrenalin group the heart weights were within normal limits. The heart weights as well as the heart weight/body weight ratios were the same in the adrenalin and in the normal group. The histologic changes in this group varied considerably. Two showed nothing either in the myocardium or in the vessels. Three showed foci of hyaline degeneration; there were variations in staining quality of the fibers in one; and, in two, the muscle stained more deeply than in the control group. One of the three had a focus of lymphocytic infiltration and small patches of early replacement fibrosis, with loose cellular connective tissue. The left ventricle in one showed slight hypertrophy. Since the left ventricle of one showed only slight hypertrophy, adrenalin in this dose over a period of twenty-six days was not enough stimulus for significant hypertrophy.

c. The heart weights of the adrenalin-thyroid group were absolutely increased. In addition, the ratio of heart weight to body weight was very significantly increased. There was hypertrophy of the left ventricle in every case. In one the hypertrophy was slight; in another, moderate; in two, moderate to marked; and, in the fifth, marked. Hypertrophy of the right ventricle was slight in two and marked in one animal. There were separation of the muscle fibers, increase in loose fibrillar connective tissue and small round cells, and polynuclear or round-cell infiltration; one had a subepicardial increase in round and spindle cells, small and large patches of replacement fibrosis as well as diffuse interstitial fibrosis, and young cellular connective tissue. In areas, hypertrophic muscle fibers showed degeneration. Some small and medium-sized arteries showed medial hypertrophy. One animal gained weight despite thyroid and adrenalin. In this one, although the heart weight was increased, the heart weight/body weight ratio was only moderately elevated. These changes appeared to occur more readily as the animal lost weight due to a severe thyroid effect. The duration of treatment played a secondary role in the production of heart muscle changes.

Group 2.—Intact animals, half given adrenalin, half adrenalin and thyroid extract.

Hearts: a. Adrenalin-Treated Group.—There was some increase in heart weight and in heart weight/body weight ratios in the adrenalin-treated animals. Of this group the right and left ventricles showed questionable microscopic fiber hypertrophy in four. There was no significant hypertrophy in one, and slight hypertrophy of both ventricles occurred in another, with the fibers markedly vacuolated and granular in the right ventricle. The septum was hypertrophied in one which had

no significant hypertrophy of either ventricle; of the two animals with some hypertrophy or microscopic changes, one had been treated for thirty-three, the other for ninety-five, days. Others treated as long as eighty days showed no changes and no hypertrophy. There were focal interstitial infiltrations of lymphocytes, histiocytes, and plasma cells in five of six animals.

b. Thyroid-Adrenalin-Treated Group.—Both the heart weights and the ratio of heart/body weight were higher in the animals which were given adrenalin and thyroid. In the thyroid-adrenalin group, there were a good-sized heart and an increase in the heart weight/body weight ratio after twenty-three days of treatment. However, as the experiment continued, the animals developed a tolerance to thyroid extract and did not lose weight, and in these the hearts were not greatly enlarged. One animal with an initial weight of 2 kilograms was allowed to gain 50 per cent of its weight; despite ninety-five days of treatment with adrenalin and thyroid extract, the heart was not hypertrophied.

Possible hypertrophy of both the right and left ventricles was noted in five. No appreciable hypertrophy occurred in another, and, in one, there was slight to moderate hypertrophy of the left, but no appreciable hypertrophy of the right, ventricle. No parallel could be drawn between the length of treatment and the degree of hypertrophy. Moderate left ventricular hypertrophy took place in an animal which was treated for twenty-three days, but not in one treated for ninety-five days. Focal interstitial infiltrations of lymphocytes, histiocytes, and occasional eosinophiles and plasma cells were present in five, and foci of early replacement fibrosis in three, out of six animals.

The hearts of the animals which received thyroid and adrenalin were individually heavier than those which were given adrenalin only. The hearts developed hypertrophy when the animal not only failed to gain, but actually lost, weight. As in the other group, an animal which lost 20 per cent of its original weight over a twenty-three-day treatment period with thyroid and adrenalin showed hypertrophy of both ventricles. Another, treated similarly for ninety-five days, gained 60 per cent of its original weight and showed no hypertrophy of either ventricle. It appeared, as in group one, that cardiac hypertrophy took place not so much from a prolonged effect as from an intensive effect of thyroid extract.

However, the striking feature of this material was the difficulty in producing significant cardiac hypertrophy in animals which were treated for three months or longer. This fact was in marked contrast to the first group of thyroidectomized animals, which were treated similarly except that an aqueous adrenalin solution instead of adrenalin in oil was used, plus the fact that in group one the animals were thyroidectomized. It appeared also that thyroidectomy sensitized the animals to thyroid

extract, for cardiac enlargement was more easily induced in the thyroidectomized than in the intact animals.

Group 3.—Thyroid-adrenalin treated animals, half thyroidectomized, half intact.

Hearts.—The right ventricle was found enlarged four times, showed little or no hypertrophy in one instance, and was regarded as normal in another. The left ventricle showed more marked changes; it was hypertrophied in every instance; once it showed slight to moderate hypertrophy, once, moderate hypertrophy, and four times, slight hypertrophy. The interventricular septum was examined in three animals. Slight hypertrophy was found in one, moderate hypertrophy in another, and no hypertrophy in the third.

Degenerative changes were more striking and seemed to be more prominent in the left ventricle. These were focal interstitial infiltration of lymphocytes and histiocytes in all the animals. Early replacement fibrosis was seen in one of the thyroidectomized group and four of the intact group.

The early response to treatment was considerable increase in heart weight and in heart weight/body weight ratios. Increase in heart weight and in heart weight/body weight ratios was progressive as the treatment period continued. There was, however, a large individual reaction to hypertrophy, and no exact correlation could be made between the grade of hypertrophy and microscopic changes and the period of treatment. It is noteworthy that an animal treated for eighteen days showed well-marked changes in both ventricles and in the septum.

In Group 3 it appears that the cardiac changes may have been less marked in the thyroidectomized group. However, loss of weight was less in this group. It has already been stated that the cardiac changes appeared proportional to the degree of loss of weight of the animals. The intact group had more frequent and greater loss of body weight, and the more marked changes in the heart were seen in animals with greater loss of weight.

Group 4 consisted of intact and thyroidectomized animals which received thyroid extract and intact animals which were given thyroid extract and adrenalin. The dose of desiccated thyroid extract and of adrenalin in oil was the same as in Groups 2 and 3. The duration of treatment was from twenty days to more than two months. All of the thyroidectomized group which received thyroid extract alone showed hypertrophy and granular and vacuolar degeneration. One of these showed perivascular infiltration, replacement fibrosis, and a few collections of lymphocytes, eosinophiles, and plasma cells. These changes were present in both ventricles and in the interventricular septum.

The group of intact animals which received desiccated thyroid extract showed less hypertrophy; one of the four showed no hypertrophy and another showed slight hypertrophy. There were granular degenera-

tion and slight increase in interstitial tissue in one, and one showed slight replacement fibrosis. Both the hypertrophy and degenerative changes were less marked than in the thyroidectomized animals.

The intact animals which received thyroid extract and adrenalin showed more marked hypertrophy and degenerative changes than the intact animals which were given adrenalin alone. Two had slight, one had moderate, and the fourth had moderate to marked, cardiac hypertrophy. Two showed degenerative changes. The one with marked hypertrophy showed fibrosis, granular and vacuolar degeneration, and infiltrations by fibroblasts.

Fig. 1.—Photomicrograph of heart muscle of thyroid-treated rabbit, showing cardiac hypertrophy, fibrosis, and cellular infiltration (×100).

In this group thyroidectomy appeared to increase greatly the sensitivity of the animals to thyroid extract. Thyroid extract produced but little change in the hearts of the intact animals, but the intact animals which received adrenalin in addition to thyroid extract showed significant cardiac hypertrophy, as well as degenerative changes in the heart muscle.

Three rabbits with spontaneous goiter, produced either by a diet consisting largely of cabbage or a diet of alfalfa hay and methyl cyanide, were studied by Dr. Marine, who kindly permitted us to examine their hearts. These goitrous rabbits were then treated with potassium iodide, and developed fulminating hyperthyroidism which resulted in death in a few weeks from loss of weight, exhaustion, and heart failure.

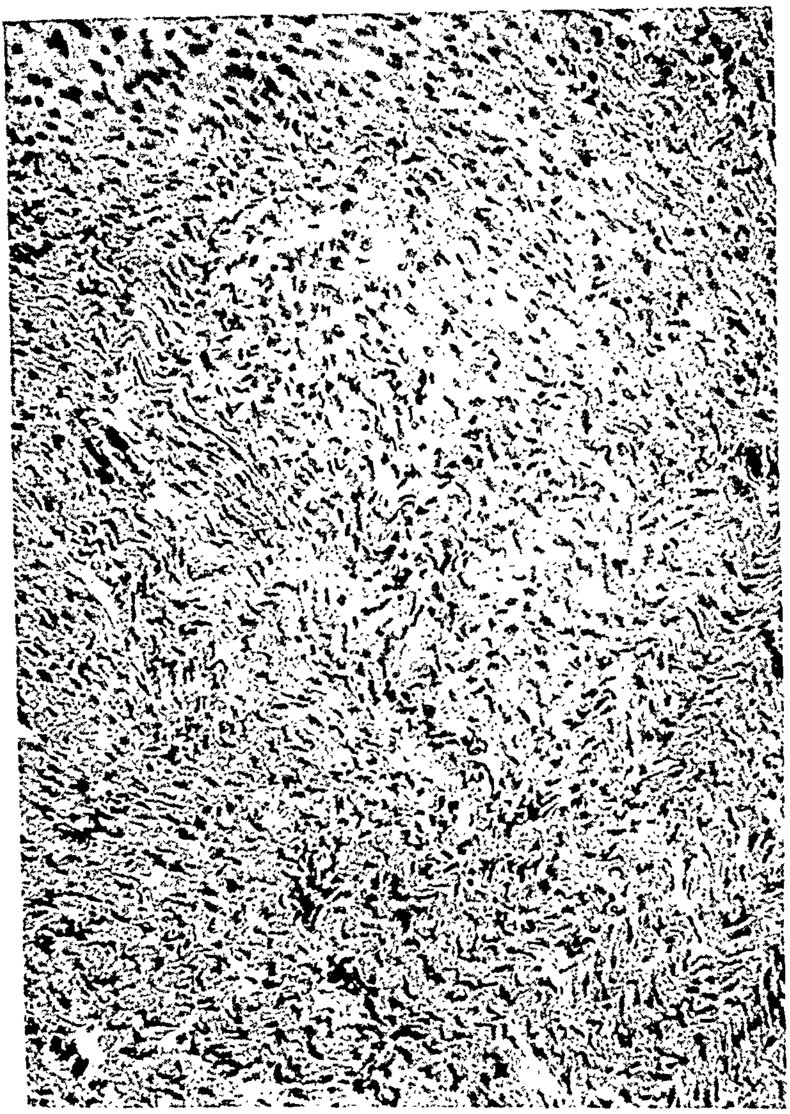

Fig. 2.—Photomicrograph of heart muscle of normal rabbit of about same weight, for comparison (×240).

The changes in the heart so resembled those in the animals which were given thyroid extract that it was deemed worth while to summarize briefly the salient features in the course of these animals.

The animal which was fed cabbage developed a large, soft goiter, measuring 3 by 4 cm. The metabolic rate was much below normal, but otherwise there were no symptoms. After three successive daily intraperitoneal injections of potassium iodide in water, the animal rapidly showed loss of weight, nervousness, restlessness, a rise in metabolic rate, and a decrease in the size of the thyroid gland. Twenty-six days after the administration of potassium iodide was started, the animal died

of hyperthyroidism. Its original weight was 2,635 grams; at death it weighed 1,505 grams, a loss of 1,130 grams, or 43 per cent of its body weight. The other two were litter mates with exophthalmos and goiter caused by the administration of methyl cyanide. A greatly enlarged right lobe of the thyroid was removed in each case, and potassium iodide administered in a dose of 21 mg. in twelve days to one, and 22 mg. in eight days to the other. Both developed tachypnea, restlessness, and tachycardia, and died two days after the potassium iodide was stopped; one of the two died of congestive heart failure. The weight had declined in one from 2,490 to 1,755 grams, a loss of 30 per cent of the body weight; and, in the other, from 2,314 to 1,642 grams, a loss of 29 per cent of the body weight.

Histologic Observations.—The heart of one weighed 8.4 Grams (body weight, 1,505 grams). The left ventricle was dilated and hypertrophied, but predominantly dilated. Microscopically, there were diffuse, marked, myocardial fibrosis, vacuolar and hyaline degeneration, and some edema. The heart of the second animal of this group weighed 7.4 grams (body weight, 1,755 grams). The organ was enlarged and the ventricles were hypertrophied; microscopically, the left ventricle showed hypertrophy, but no degenerative changes. The right ventricle showed hypertrophy of the muscle cells, which were separated by bluish staining edematous material and some areas of cellular infiltration. The heart of the third rabbit of this group weighed 9.1 grams (body weight, 1,642 grams). The organ was moderately dilated, all chambers were filled with semiclotted blood, and the papillary muscles were slightly mottled. Microscopically, the right ventricle showed hypertrophy of the muscle fibers, with degeneration, edema, fibrosis, and some cellular infiltration. The left ventricle showed similar changes, except that they were more marked and the fibrosis was greater.

Chesney, Clawson, and Webster[20] observed the development of large goiters in rabbits on cabbage diets. They found that heat production in goitrous rabbits was below normal, and that there was an inverse relationship between the size of the thyroid gland and the metabolic rate. Marine, Baumann, and Cipra[21] showed that the substance responsible for cabbage goiter is probably a cyanide. The extremely small amount of iodine which will cause fatal hyperthyroidism in a goitrous rabbit is noteworthy.

In some rabbits with goiter, Webster and his co-workers[22] observed a sudden increase in heat production before death. Some animals showed a rise in metabolic rate which was too great to be accounted for by mere loss in body weight. Unlike humans, who usually show a decrease in metabolic rate and a gain in body weight after the administration of iodine, in goitrous rabbits there is a rise in metabolic rate, with loss of body weight and death in a few days.

These three animals, despite the fact that exophthalmos and goiter had been present for a long time, maintained themselves well until iodine was given. The dose was not large, and, in two, hemithyroidectomy was performed in an effort to control hyperthyroidism. The excised lobes showed marked enlargement, greatly increased vascularity, and marked hyperplasia, Despite the evidence of involution of the thyroid gland after treatment and hemithyroidectomy, small doses of iodine produced a rapidly fatal course of hyperthyroidism.

The counterpart in man is not lacking, for certain persons develop Graves' disease after the administration of iodine; this is referred to as iodine Basedow's disease. Benign, human, adenomatous goiter may also become toxic on the administration of iodine, and behave like typical Graves' disease. Such a course is a direct counterpart of the animal experiment. However, the fact that goitrous rabbits develop hyperthyroidism when they receive iodine, whereas humans commonly show a fall in metabolic rate, is a noteworthy point of difference. Furthermore, humans with toxic goiter frequently improve or are cured after subtotal thyroidectomy, but, in two of the three rabbits, hemithyroidectomy did not lessen the course of fatal hyperthyroidism.

The changes in the hearts of rabbits with induced hyperthyroidism are, however, different from those in humans with Graves' disease or hyperthyroidism. Cardiac hypertrophy in animals is marked, but, in humans, cardiac dilatation may be marked, but hypertrophy is rare. In fact, in human Graves' disease, when cardiac hypertrophy is found, it is usually due to some other cause, most commonly rheumatic heart disease or hypertension. Goitrous rabbits probably develop "goiter heart," with cardiac hypertrophy, because the large goiter acts as a reservoir for blood and acts in the same way as an arteriovenous fistula. In the goitrous rabbits which were given small doses of iodine, fatal hyperthyroidism was associated with greatly intensified effects on the heart, as evidenced by marked cardiac hypertrophy and myocardial changes.

DISCUSSION

Thyroid extract inhibits body growth. At the same time, it causes hypertrophy of the liver, spleen, kidneys, adrenals, and heart. Although Hoskins did not find it always, the growth-inhibiting effect of thyroid was constant in our material and in that of Cameron and Carmichael.[3] The inhibition of body growth, on the one hand, and hypertrophy of the heart, on the other, were constant and parallel effects, providing the doses of thyroid were large enough. Cardiac hypertrophy and loss of weight could be produced at will, and were directly proportional to the dose of thyroid. However, after the thyroid had been given for a time, it became much less effective because of the development of a tolerance for the drug.

In the animals that developed cardiac hypertrophy, which at times followed treatment with adrenalin alone and was common in the animals which received both thyroid and adrenalin, there appeared to be a fairly high heart weight/body weight ratio. However, there was a fall in the ratio about the third or fourth week of the treatment. Subsequently, there was a rise again. Stewart,[10] who produced cardiac hypertrophy by injections of adrenalin, made similar observations, and was of the opinion that the early stage of cardiac hypertrophy was due to an increase in the content of water, and that, after the third week of adrenalin injections, the edema disappeared. Since we observed a high heart weight/body weight ratio in the early phase of treatment, which subsequently became lower and then higher as treatment was continued, it appears that the early phases of cardiac hypertrophy may be associated, as Stewart[10] thought, with water retention, and is followed by an increase in muscle mass. However, since the animals which were treated for more than three or four weeks may have developed a tolerance to thyroid extract, this factor, rather than alteration in water content of the myocardium, may explain the later reduction in the heart weight/body weight ratio.

The two recognized views concerning the pathogenesis of cardiac hypertrophy are that it is caused by work or tissue injury. Adrenalin and thyroid can induce hypertrophy from a physiologic point of view by increasing work, as well as by tissue injury. There was no exact relationship of heart weight and tissue injury to the duration of treatment. Nevertheless, the extent of myocardial damage and hypertrophy was greater in the animals in which an intense thyroid effect was obtained, especially if it was maintained over a long period of time. Tachycardia, anoxemia, and thickness of muscle fibers may also play a role. Since both thyroid and adrenalin caused myocardial fibrosis and hypertrophy, it is undeniable that the histologic changes may be the direct result of the treatment, independent of hypertrophy. Myocardial scarring may be the result, or the cause, of cardiac hypertrophy. It is interesting that Simonds and Brandes[6] observed cardiac hypertrophy in animals that had lost 25 to 35 per cent of their body weight. When the body weight loss was greater, the heart lost some of the weight it had gained as a result of hypertrophy.

Hashimoto[4] observed dilatation, especially of the right ventricle, in thyroid-fed rats; this was more marked in the male animals. Although we agree in large part with him, we, like Simonds and Brandes, observed, in contradistinction to his results, that the left ventricle was more affected than the right. In fact, when the right ventricle showed muscle hypertrophy, fibrosis, or infiltration of different types of cells, the changes were usually present and more marked in the left. When hypertrophy or fibrosis was minimal, cardiac hypertrophy was often limited to the left ventricle.

In the animals in this series which showed loss of body weight, the actual weights of the hearts, as well as the heart weight/body weight ratios, were high. On the other hand, in the animals which did not lose much weight, or actually gained weight, the heart weights were not significantly increased, the heart weight/body weight ratios were not high, and histologic changes in the hearts were not marked. These observations corroborate the view that it is the intensity of treatment with thyroid extract that is responsible for the degree of cardiac hypertrophy and the severity of the associated histologic changes.

Brown, Pearce, and Van Allen[23] ascertained organ weights and their ratios to body weights in a large number of normal rabbits. We have made a similar study (Table II) in a comparable series. They found that the ratios of heart weight to body weight were from 0.202 to 0.282; the majority were about 0.230. Our observations were roughly similar. It is noteworthy that, in our animals in which the thyroid effect was

TABLE II

BODY WEIGHTS, HEART WEIGHTS, AND HEART WEIGHT/BODY WEIGHT RATIOS OF NORMAL RABBITS OF VARIOUS BODY WEIGHTS

BODY WEIGHT	HEART WEIGHT	HEART WT./BODY WT. RATIO
Under 1500 Gm.		
1426	3.6	0.250
1500-2000 Gm.		
1977	5.9	0.282
1712	3.6	0.210
1735	4.8	0.277
1998	5.1	0.255
1660	4.9	0.295
2000-2500 Gm.		
2233	5.4	0.242
2062	5.3	0.257
2203	4.7	0.213
2256	4.5	0.200
2208	4.0	0.181
2130	5.1	0.239
2297	4.6	0.200
2105	5.4	0.256
2100	5.3	0.252
2242	5.4	0.241
2287	5.0	0.219
2396	5.8	0.242
2451	6.1	0.249
2500-3000 Gm.		
2564	5.2	0.203
2574	6.0	0.234
2710	6.1	0.225
2650	6.3	0.237
2800	6.4	0.228
2888	6.0	0.208
2595	4.8	0.185
2671	6.3	0.236
2896	4.5	0.155
2702	3.6	0.133
2772	6.2	0.220
2570	5.4	0.210
Over 3000 Gm.		
3150	8.1	0.256
3450	8.2	0.237

marked, there was an increase in heart weights, and the ratios of the heart weights to body weights were much higher than these figures.

Corroborative evidence to show that these data represent an intrinsic increase in heart weight due to cardiac hypertrophy are available from starvation experiments. Voit[25] found that the heart of a cat lost only 3 per cent of its weight during such an experiment, whereas other organs lost much more. Morgulis,[24] however, feels that Voit's[25] results are open to question because they have not been confirmed by other investigators. From Morgulis'[24] tabulation of many investigations on various animals, it is evident that the proportion of heart weight to body weight after starvation is higher than in the normal animal, indicating that the heart loses less than other organs. Nevertheless, the disproportionately smaller loss of the heart as compared to other organs does not explain the high heart weight/body weight ratios in our animals.

Simonds and Brandes[6] made calculations from the data of Junkersdorf[26] on starved dogs, and found a correlation between body weight and heart weight in normal animals and, also, that the coefficient of correlation between heart weight and final body weight in starvation was only slightly less than normal, indicating that in starvation the heart loses weight in almost the same proportion as the body as a whole. Since both the heart weights and the heart weight/body weight ratios were increased in our animals, we may say that they were not increased merely from inanition. If we assume that the heart does not lose weight as rapidly as the rest of the body, a high heart weight/body weight ratio is explicable, but this would not account for the actual increase in the heart weights of our thyroid-treated animals. Simonds and Brandes[6] showed that, in experimental hyperthyroidism in dogs, the mean, minimum, and maximum heart weight to final body weight ratios were considerably higher than in starved dogs. They also showed that the coefficient of correlation between heart weight and final body weight was less in experimental hyperthyroidism, indicating that the heart does not lose to the same extent as the rest of the body. This failure of the heart to lose is due to actual hypertrophy of the heart caused by thyroid extract or a combination of thyroid extract and adrenalin.

SUMMARY

Adrenalin in oily or watery solution, alone and in combination with thyroid extract, was administered to thyroidectomized and intact rabbits over varying periods of time. It was not possible to produce more than slight cardiac hypertrophy and myocardial degeneration with adrenalin, but the synergism between thyroid and adrenalin resulted in much more marked cardiac hypertrophy, myocardial fibrosis, and infiltrative lesions.

Thyroidectomy appeared to sensitize the animals to the effects of thyroid extract. Cardiac hypertrophy and myocardial damage were more marked in the thyroidectomized than in the intact animals which received thyroid, or thyroid and adrenalin. Treatment with an aqueous solution of adrenalin and thyroid resulted in much more marked effects on the heart than the slower, more prolonged, oily adrenalin solution and thyroid extract.

Cardiac hypertrophy is contingent, not so much on a prolonged, as on an intense, effect of thyroid extract which is associated not only with a failure to gain, but is accompanied by a loss of about 25 per cent or more of the original body weight. When cardiac hypertrophy develops, there is an early rise in the heart weight/body weight ratio. Whether there was, as Stewart thought, an initial rise in heart weight caused by fluid retention, followed by an increase in muscle mass, is not possible to state. In our animals which were allowed after three or four weeks of treatment to maintain, rather than forced to lose, weight, there was a fall of the heart to body weight ratio. We believe that the fall in ratio after an initial rise was not necessarily caused by edema of the heart followed by an increase in the muscle mass. The fall may have been due to the fact that the thyroid effect was not intense enough to stimulate the development of cardiac hypertrophy.

A tolerance is quickly developed to thyroid extract in fairly large doses, and, when the effects of the drug have disappeared, they can be restored, as desired, by increasing the dose.

The clinical course of, and necropsy observations on, three rabbits with cabbage goiter, which developed fatal hyperthyroidism after small doses of iodine, are discussed. Although hemithyroidectomy was performed in two instances, and iodine was stopped in all three cases, the alteration from hypothyroidism to hyperthyroidism was rapidly fatal in all.

We wish to acknowledge our indebtedness to Dr. David Marine and Dr. Samuel H. Rosen for operating on the animals and for much help with all the experiments, and to Dr. Louis Leiter for suggestions in the preparation of this paper.

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THE PRESENCE OF ELECTROCARDIOGRAPHIC CHANGES IN NICOTINIC ACID DEFICIENCY AND THEIR ELIMINATION BY NICOTINIC ACID

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THE only vitamin deficiency so far known to be associated with cardiovascular disturbances is that of vitamin B_1, e.g., beriberi heart disease, which is manifested by cardiac enlargement and heart failure. Cardiac insufficiency caused by vitamin B_1 deficiency may occur also in alcoholic addicts, together with other manifestations of avitaminosis B_1 (Weiss and Wilkins[1]). In such cases, vitamin B_1 administration promptly results in clearing up the cardiac failure and in a decrease in the size of the heart.

Cardiovascular symptoms have also been observed in another type of B avitaminosis, namely, pellagra, particularly in the acute form. The symptoms consist mainly of dyspnea on exertion and palpitation. Cardiac enlargement and failure are not, however, mentioned as a special feature of pellagra. Electrocardiographic studies in pellagra have disclosed abnormalities in a large percentage of cases, consisting mainly in alteration of the S-T segment and inversion of the T wave (Feil[2]). Since, in deficiency diseases in man, several factors of the vitamin B complex may be lacking simultaneously, and since vitamin B_1 deficiency is known to be associated with changes in the electrocardiogram, the electrocardiographic changes found in pellagra were attributed to B_1 deficiency. Mainzer and Krause[3] found a high incidence of abnormal electrocardiograms in pellagrins in Egypt, but believed that these changes were not characteristic of pellagra, and that their occurrence was not sufficient to conclude that they are caused by deficiency of nicotinic acid. As there was a parallelism between the course of the disease and the electrocardiographic changes, which disappeared rapidly in one case after nicotinic acid therapy, they assumed that a causal relationship may exist between these changes and the pellagra.

In this paper we report the effect of nicotinic acid on the electrocardiograms in two cases of nicotinic acid deficiency. Both patients presented the typical picture of pellagra, including pellagra dermatitis, and responded to treatment. A year later in one case, and six months later in the other case, all of the visceral manifestations of pellagra reappeared, but pellagra dermatitis was absent. In both cases there were marked abnormalities in the electrocardiograms, and in both instances

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Received for publication March 11, 1943.

a series of experiments was carried out to ascertain whether or not the nicotinic acid had a specific effect on the electrocardiographic changes.

REPORT OF CASES

Case 1.—A 30-year-old woman who had been suffering from repeated attacks of diarrhea for many months was admitted in a state of severe deficiency. She had stomatitis, glossitis, severe diarrhea, marked anemia, and mental disturbances. There was marked edema of the lower extremities, as well as neuritic manifestations. The patient complained of palpitation and precordial pain. The heart was normal in size, and there were no signs of cardiac insufficiency. The heart sounds were feeble, the pulse rate accelerated, and the blood pressure, 110/80.

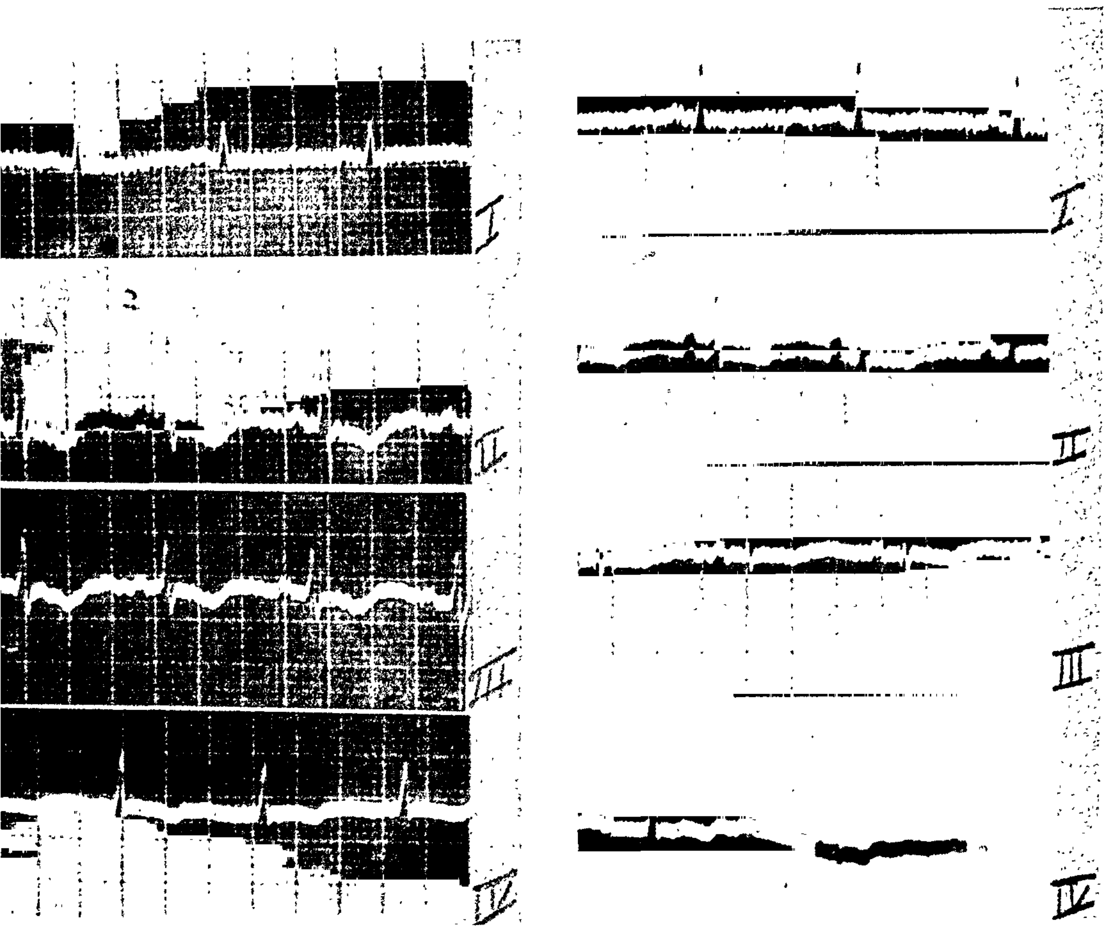


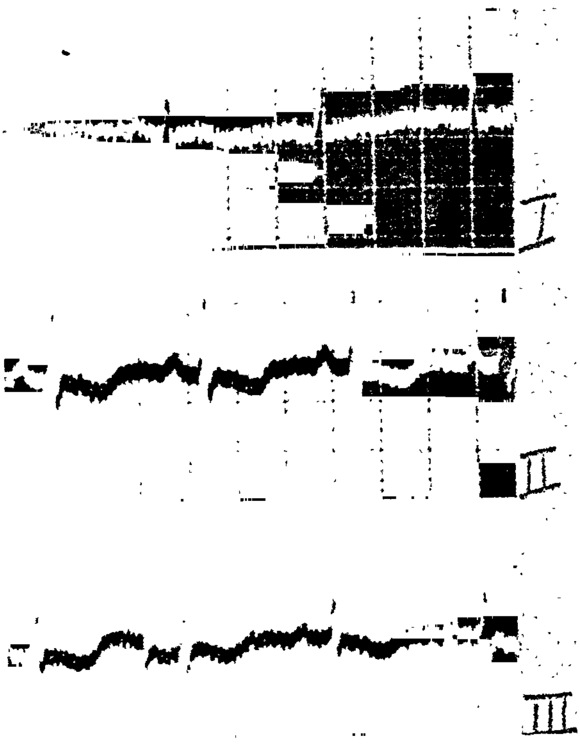
Fig. 1*A*. Fig. 1*B*.

Fig. 1*A*.—Electrocardiogram taken before treatment. Flat T_1 and inverted T wave in Leads II, III, and IV.

Fig. 1*B*.—After six days of treatment with nicotinic acid. T wave in Leads II, III, and IV slightly inverted.

The first electrocardiogram (Fig. 1*A*) showed marked changes, namely, a flat T_1 and an inverted T_2, T_3, and T_4. The patient was given an ordinary diet, plus 500 mg. of nicotinic acid daily by mouth. Her mental symptoms, stomatitis, and glossitis responded promptly; also, the diarrhea diminished in severity. An electrocardiogram taken six days after

the beginning of treatment (Fig. 1*B*) showed marked improvement. The T waves were now only slightly depressed in Leads II and III, and not inverted as before. Nicotinic acid was now discontinued, and, during the following five days, only vitamin B_1 was given (40 mg. daily, intravenously). This change in treatment was followed by an increase in diuresis and subsidence of the edema, but the mental and gastro-intestinal disturbances became worse. Another electrocardiogram (Fig. 1*C*) disclosed that the abnormalities which were present on admission



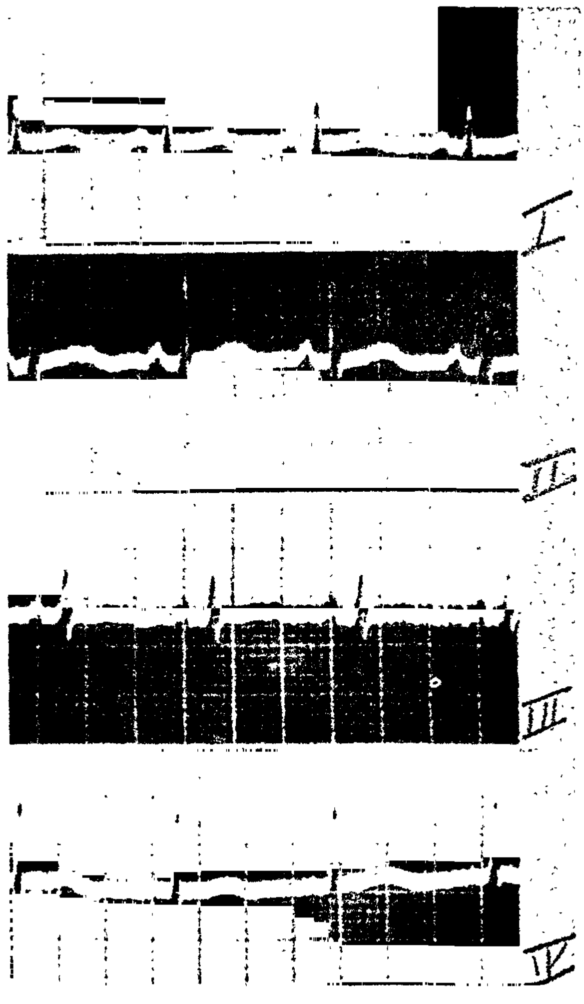


Fig. 1*C*. Fig. 1*D*.

Fig. 1*C*.—Nicotinic acid discontinued. Only B_1, 40 mg. daily, given. Electrocardiographic changes similar to Fig. 1*A*.

Fig. 1*D*.—After fourteen days of renewed nicotinic acid administration, practically normal electrocardiogram.

had reappeared. Nicotinic acid was again given, with the result that, a fortnight later, a practically normal tracing was obtained. The T waves became positive in Leads I, II, and IV, and isoelectric in Lead III (Fig. 1*D*). Intercurrent infections repeatedly exacerbated the deficiency state, in spite of continuous nicotinic acid administration. These exacerbations and the improvement which followed them were reflected in the subsequent electrocardiograms.

Case 2.—The patient was a 50-year-old man who was suffering from intestinal amebiasis. The first attack occurred in the summer of 1941. After three months of continuous diarrhea, the patient developed the

typical signs of pellagra; the latter responded promptly to nicotinic acid. In February, 1942, he again had an attack of diarrhea, which, after one month, produced a severe deficiency state. The patient was readmitted to the hospital March 26. This time all the visceral manifestations of nicotinic acid deficiency were present, particularly gastrointestinal and mental disturbances, but no cutaneous lesions were present. The patient was emaciated and dehydrated. The pulse was slow and feeble, the heart sounds dull. The heart was normal in size, both on clinical and fluoroscopic examination. The blood pressure was 85/80. There were no signs

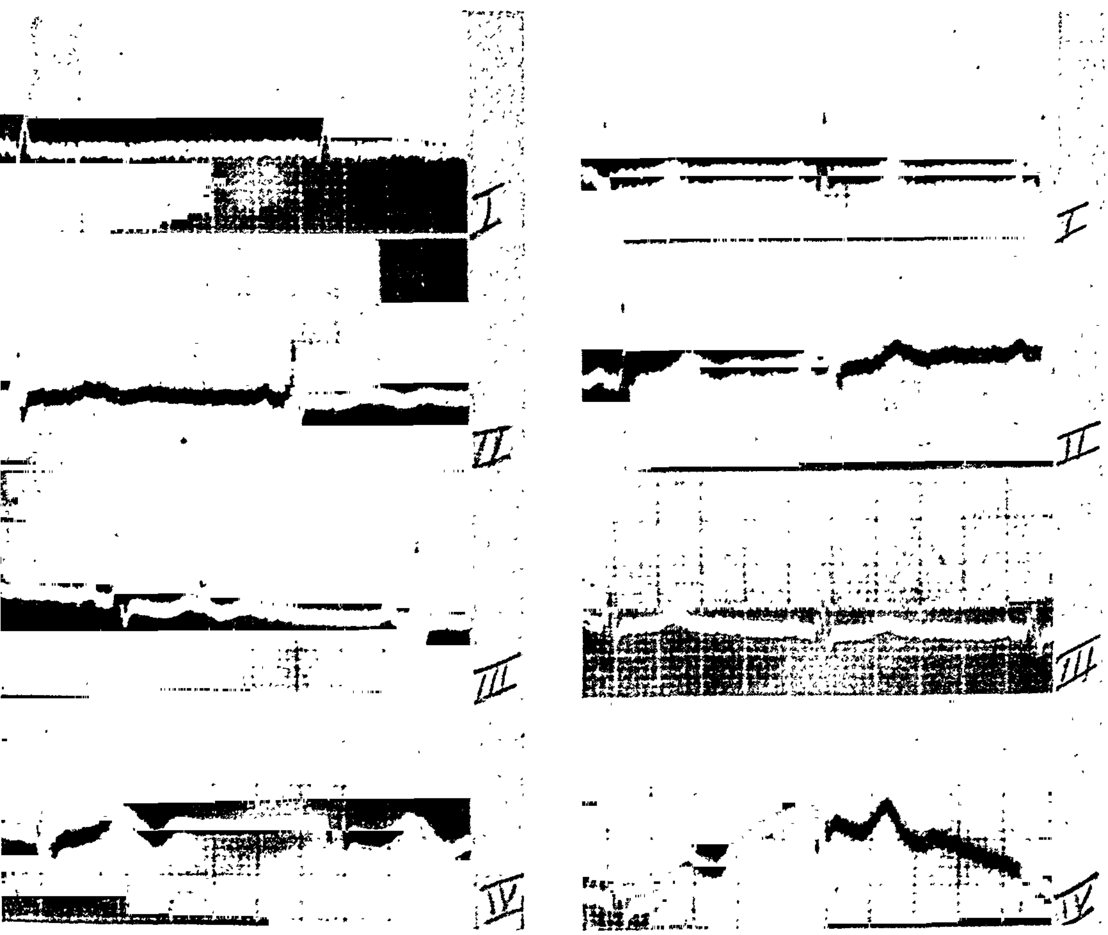


Fig. 2A. Fig. 2B.

Fig. 2A.—Marked changes in the T wave in all leads.
Fig. 2B.—After six days of treatment with nicotinic acid, electrocardiogram normal.

of heart failure and no edema was present. The electrocardiogram, however, disclosed pronounced changes in the T waves in all leads (Fig. 2A). The patient was first given a continuous intravenous infusion of saline (4 liters in three days). His condition improved noticeably, although the diarrhea continued and the condition of the tongue and mouth did not change. The second electrocardiogram, made March 31, showed the same changes as before. Nicotinic acid treatment was now begun. The patient was given 500 mg. of nicotinic acid by mouth and 100 mg. intravenously for six days, together with an ordinary mixed diet. At the end of this period the diarrhea stopped completely and the

appearance of the mucous membrane of the tongue and the buccal parts of the lips improved considerably, although he still complained of soreness and a burning sensation. The electrocardiogram made on April 7 (Fig. 2*B*) was perfectly normal. The T waves had become upright in all leads. The patient remained in good condition in spite of discontinued medication, and his electrocardiograms also remained normal. Thus, in this case as in the preceding one, the administration of nicotinic acid had a prompt and definite effect on the heart, as evidenced by the electrocardiograms.

COMMENT

Therapeutic tests in our cases justify the conclusion that the electrocardiographic changes which occur in pellagra are due specifically to nicotinic acid deficiency. In both cases the changes in the electrocardiogram were shown to be reversible.

What explanation can be offered for the direct effect of nicotinic acid on the heart?

Nicotinic acid is known to produce vasodilatation of the skin, as indicated by flushing in various parts of the body after administration of this drug. It is conceivable that nicotinic acid has the same effect on the coronary vessels, thus increasing the blood supply of the heart. But it is doubtful whether blood vessels of visceral organs are at all affected by nicotinic acid. Investigations have shown that the blood flow through the brain is hardly increased by this substance,[4] although the pial vessels were found to be dilated.[5] Furthermore, the vasodilator action of nicotinic acid is, in general, transient in character; flushing of the skin usually disappears within half an hour.[6] It seems likely, therefore, that the influence of nicotinic acid on the electrocardiographic changes is due to some more fundamental action.

The most conspicuous changes produced in the electrocardiogram by nicotinic acid were observed in the T wave. Inasmuch as metabolic changes in the heart muscle are reflected in the T wave (anoxemia, thyroid deficiency, and avitaminosis B_1), any factor affecting the metabolism of the heart muscle may affect also the character of the T wave.

Nicotinic acid is the chemically active fraction of the coenzymes which are essential for the intermediate metabolism of carbohydrates. A marked diminution of coenzyme I in the striated muscle of human subjects, produced by deficiency of nicotinic acid, was recently reported by Axelrod, Spies, and Elvehjem,[7] who assume that the decrease in the coenzyme content may affect the ability of the human muscle to carry out its oxidative function. The symptoms and signs of avitaminosis are regarded as the results of chemical disturbances of cellular function due to failure of coenzyme (Sydenstricker[8]). It seems logical, therefore, to assume that an altered metabolic state of the heart is due to coenzyme deficiency; the resulting changes are reversible, i.e., they disappear promptly after the administration of nicotinic acid.

SUMMARY

Two cases of nicotinic acid deficiency are reported; in both there were marked changes in the electrocardiograms, particularly in the T waves. Nicotinic acid administration resulted in prompt improvement in the nature of the electrocardiographic pattern, thus suggesting a specific effect of nicotinic acid on the heart, most probably the heart muscle.

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A-V BLOCK IN A-V NODAL RHYTHM

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AURICULOVENTRICULAR rhythm (A-V nodal rhythm) is that rhythm in which the pacemaker controlling the entire heart resides in the A-V nodal tissue. A-V nodal rhythm was recognized and classified as upper, middle, and lower nodal rhythm as a result of animal experiments[1-6] which demonstrated that the time relationship of auricular and ventricular activity depended on the site of impulse formation within the A-V node.

In the human electrocardiogram the diagnosis of A-V nodal rhythm is made on the basis of the P-R duration and the pattern and direction of the P wave. The P-R interval may vary from 0.12 second* to a negative value (an R-P interval). The P wave, which is of retrograde character, tends to be inverted in Leads II and III, and small and upright in Lead I.[8] In exceptional instances, an upright P wave occurs in all the limb leads, with a P-R interval of less than 0.12 second; such rhythms are classified as A-V nodal rhythm.[9, 10] In these cases the pacemakers must be located closer to the ventricles than the sinus node, presumably in the A-V node; otherwise, we must assume that a special, fast-conducting path exists between the sinus pacemaker and the ventricles. If these are A-V nodal in origin, the absence of a retrograde pattern could be due to intra-auricular block, making the path resemble that of sinus beats, or to the fact that the part of the A-V node which gives rise to the beat lies in such a position with respect to the sinus node as to lead to a spread in the auricles similar to that from the sinus node. This latter and more likely possibility could apply only to those strands of the A-V node which surround the coronary sinus and lie to its right. It is for this reason that this type of nodal rhythm has been regarded by us as exemplifying so-called coronary nodal rhythm. Others[11, 12] have attributed such rhythms to pacemakers in dispersed islets of specific muscular tissue in the auricles. There are animal experiments to show that the P wave in A-V nodal rhythm need not be inverted,[13] and that inverted P waves may occur in sinus rhythm with intra-auricular block.[14, 15] A special group of cases has been described as coronary sinus nodal rhythm[16] when P is inverted and P-R is longer than 0.12 second, but the experimental evidence for this classification

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Aided by the A. D. Nast Fund for Cardiovascular Research.

Received for publication March 13, 1943.

*We are excluding from this discussion cases of short P-R and prolonged QRS of the type described by Wolff, Parkinson, and White,[7] which have been given various interpretations.

has been questioned.[17] Wenckebach and Winterberg[18] believe that it is impossible to separate the different portions of the A-V node functionally or anatomically. They follow the terminology of Clerc and Pezzi[19] in classifying both upper nodal, and so-called coronary nodal, rhythms as supranodal rhythm.

In most classifications of nodal rhythm the assumption is made that the impulse spreads at normal speed toward both the auricles and ven-

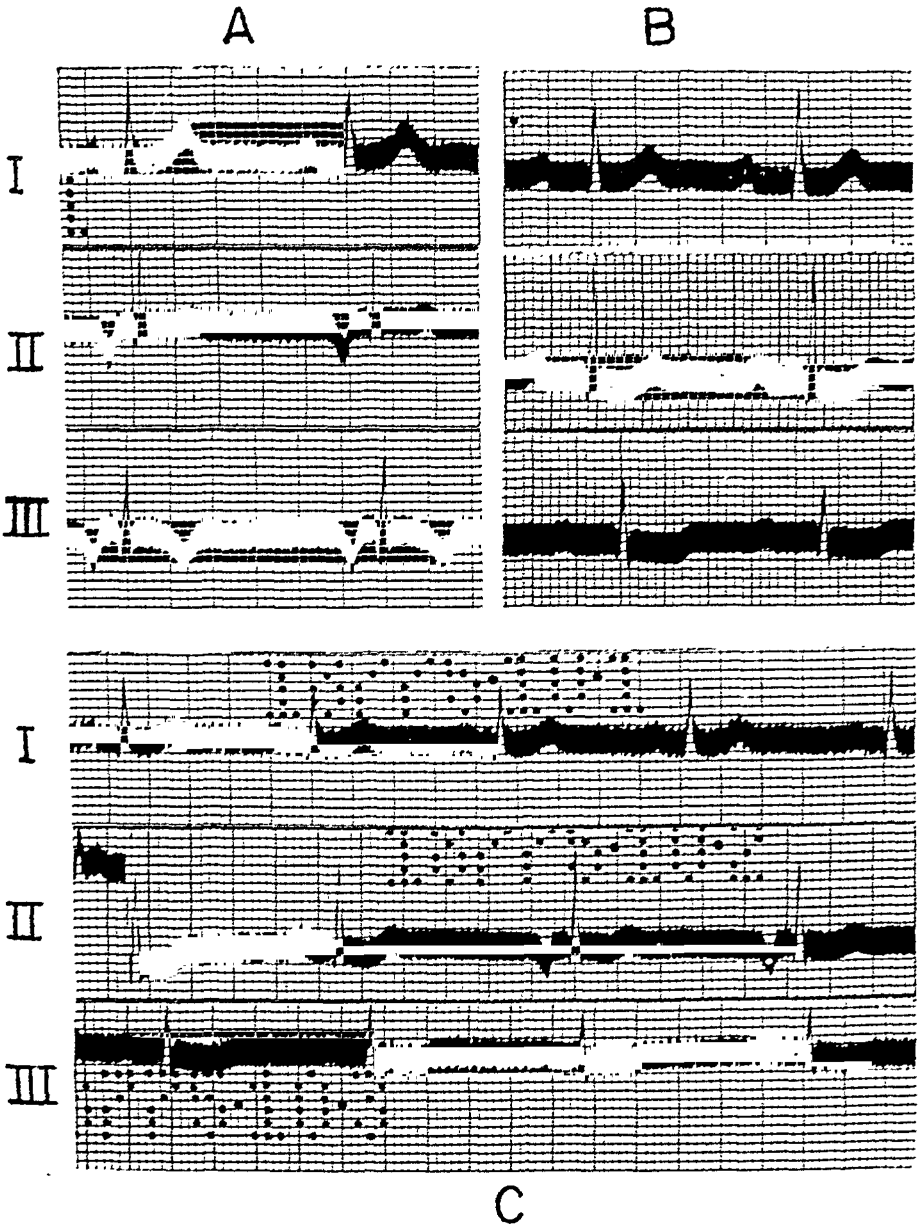

Fig. 1.—In segment *A*, Lead I shows an upright P wave preceding the QRS (P-R interval) by 0.22 second. The rate is 60, and regular. Leads II and III show an inverted P wave preceding the QRS (P-R interval) by 0.18 second. The rate is irregular and averages 55. Segment *B*, taken six weeks after *C*, shows upright P waves in all limb leads, with a prolonged P-R interval of 0.26 second. The rate is fairly regular at 65. Segment *C*, taken five months after *A*, shows an upright P wave in Leads I and III, with a P-R interval of 0.21 second and an average rate of 62. In Lead II the first two ventricular complexes are preceded by an upright P wave, with a P-R of 0.21 second; following this, the P wave is inverted and the P-R interval 0.16 second. Discussed in text.

tricles from the site of impulse formation. Evidence has accumulated, both in animal experiments[13, 20-22] and in the analysis of human electrocardiograms,[23, 24] that delay, or even complete blockage, of the A-V nodal impulse on its way to the ventricles (antegrade block) or on its way to the auricles (retrograde block) occurs. It is evident that, under these circumstances, the usual criteria for the diagnosis and classification

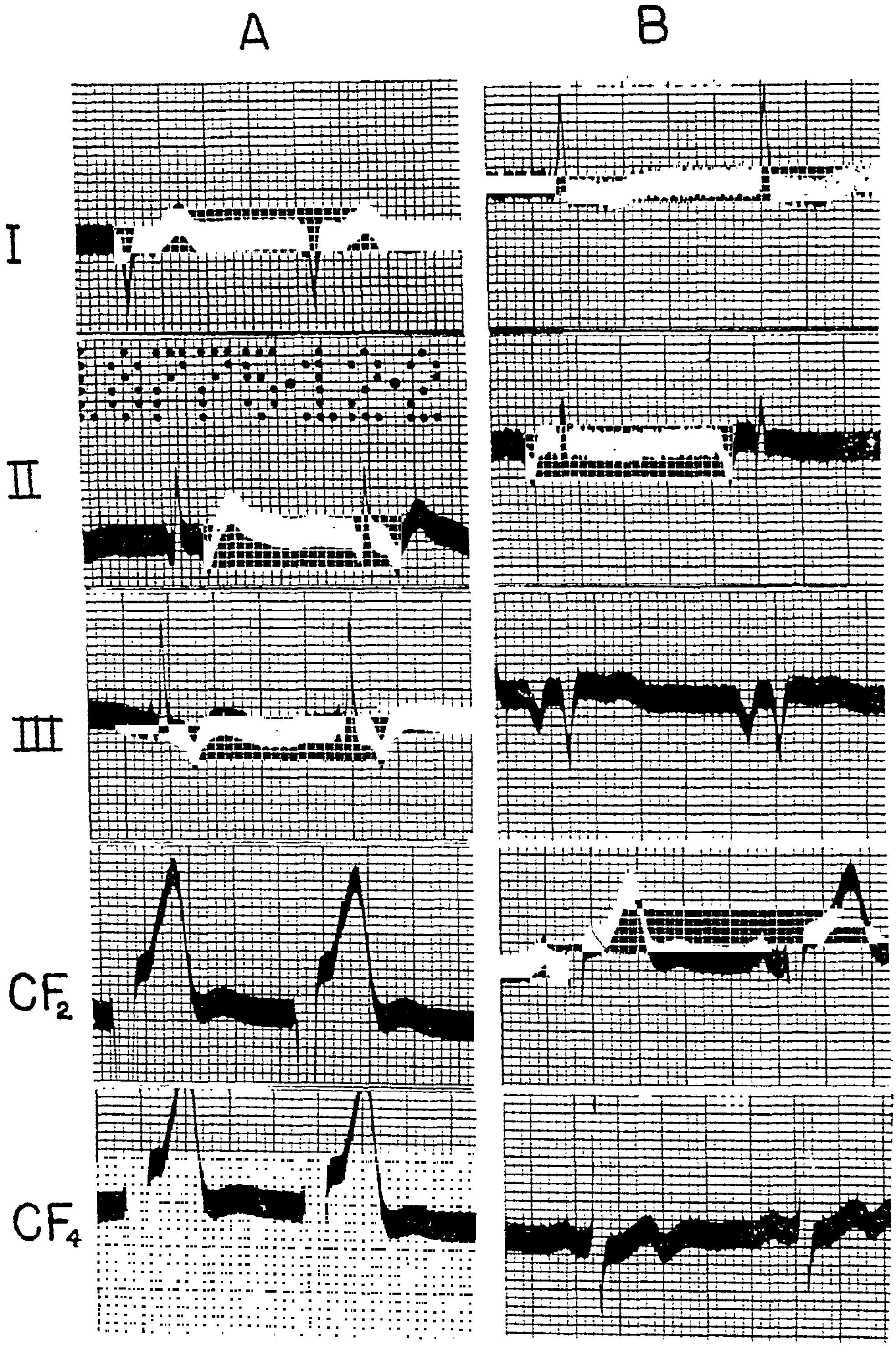

Fig. 2.—In segment *A*, taken five weeks after Fig. 1, *C*, the QRS duration was 0.12 second. An inverted P wave following the QRS at an R-P interval of 0.16 second is seen in all limb leads. The rate is 72. Segment *B*, taken two days after *A*, shows an inverted P wave in Leads II and III preceding the QRS at a P-R interval of 0.16 second. In Lead I the P wave is indiscernible. P is upright in CF_2 and CF_4. The rate is 66. Discussed in text.

of A-V nodal rhythm need not apply.[6, 25-27] In this report, a series of electrocardiograms is presented to illustrate this fact.

The records were obtained on a 49-year-old white man who had been suffering from attacks of angina pectoris for two years prior to his entry into the hospital in April, 1942. The electrocardiograms presented in Figs. 1 and 2 were taken over a period of seven months, and the last one, Fig. 2, *B*, was taken forty-eight hours before the patient's death. Autopsy revealed severe sclerosis and narrowing of both left and right coronary arteries, with recent, extensive infarction of the left ventricle and interventricular septum.

The mechanism in Fig. 1, *B* is obviously sinus rhythm, with first degree A-V block. Fig. 1, *A* and *C* shows the transition from upright P waves, with P-R prolonged to 0.21 and 0.22 second, to inverted P waves with P-R intervals of 0.18 and 0.16 second; the upright P waves in Fig. 1, *C* resemble those of corresponding leads in Fig. 1, *B*. It seems logical, therefore, to conclude that Fig. 1, *A* and *C* is an example of transition from sinus to A-V nodal rhythm in the presence of first degree A-V block. In this instance, the long P-R intervals which follow the inverted P waves in Leads II and III, 0.18 and 0.16 second, respectively, are therefore due to the A-V block in the presence of A-V nodal rhythm, and not to, the alternative explanation, sinus rhythm with intra-auricular block of such a nature as to invert the P waves.

The inverted P waves in Fig. 2, *B* resemble those in Fig. 1, *A* and *C*, and the P-R interval is of the same order, i.e., 0.16 second. It is therefore apparent that the heart, at the time Fig. 2, *B* was recorded, was controlled by a subsidiary pacemaker in the A-V node; prolongation of the P-R interval beyond the accepted upper limit for A-V nodal rhythm again results from A-V block, as it did when tracings 1, *A* and *C* were recorded. This suggests that every instance of a rhythm with sharply inverted P waves in Leads II and III, accompanied by a P-R interval of more than 0.12 second, represents A-V nodal rhythm with A-V block, rather than sinus rhythm with intra-auricular block.

Since the P-R interval in A-V nodal rhythm may be longer than 0.12 second, the subdivisions of A-V nodal rhythm may not be justified; antegrade or retrograde block can lead to different P-R intervals as readily as can different locations of the pacemaker in the A-V node (Fig. 3). In A-V nodal rhythm the P-R interval is, of course, equal to the conduction time from the pacemaker to the auricles, less that from the pacemaker to the ventricles. A positive P-R means that the antegrade conduction time exceeds the retrograde, and a negative P-R (an R-P interval) means the reverse. Regardless of the location of the A-V nodal pacemaker, block below it may lead to a positive P-R interval, and block above it may lead to a negative P-R interval. In fact, complete block above the A-V nodal pacemaker would abolish retrograde P waves; the auricles would be at a standstill or under the control of

some other pacemaker. The assumption in this, as in other forms of A-V nodal rhythm, is that the sinus node is inactive or that its impulse cannot get through an S-A block. Likewise, in complete block below the A-V nodal pacemaker, there would arise a most peculiar condition, with the auricles under the control of the A-V nodal pacemaker and the ventricles under the control of another (idioventricular) pacemaker.

Furthermore, if first degree blocks exist both above and below the A-V nodal pacemaker, their relative severities will determine the position of P with regard to QRS (Fig. 3). In our particular case, the simplest explanation is that the prolonged P-R interval in the records with A-V nodal rhythm was caused by block in the A-V junctional tissues, exclusively or predominantly below the site of nodal impulse formation.

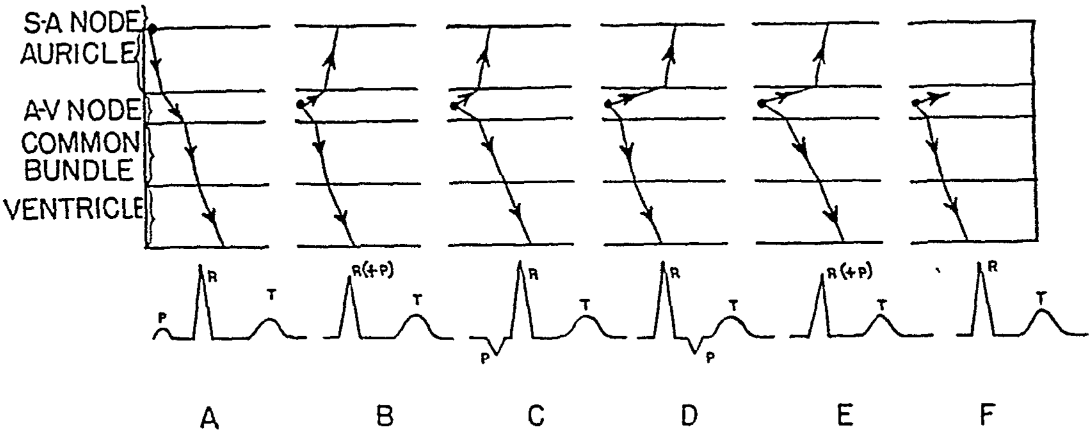

Fig. 3.—Diagram illustrating effect of A-V block on A-V nodal rhythm. *A* represents sinus rhythm; *B*, A-V nodal rhythm so located that the impulse reaches auricles and ventricles simultaneously. *C*, *D*, *E*, and *F* represent A-V nodal rhythm originating in the same site as *B*, but with A-V block present. In *C*, the block is incomplete and located below the pacemaker; in *D*, it is above the pacemaker; in *E*, it is both above and below the pacemaker and of such degree that the impulse reaches the auricles and ventricles simultaneously. In *F*, the block is above the pacemaker and is complete. Diagrammatically, in each segment the pattern of spread is indicated above (arrows showing direction) and the electrocardiogram below. In the upper part, the various parts of the heart through which the impulse may spread are indicated by labeling at the left, the horizontal lines serve to separate these, and their intersection by the inclined lines indicates the time the impulse arrives at each region. Dots show location of pacemaker; inclination of lines leading from it shows the rate of conduction. In the electrocardiogram, P, QRS, and T are labeled, and the letter R is used to indicate QRS. The inverted P wave indicates retrograde P; where P coincides with QRS this is indicated by R (+P). Discussed in text.

It is necessary to account for the fact that, in Fig. 1, *A* and *C*, the P-R interval of the A-V nodal rhythm is shorter than that of the sinus rhythm. Of the three factors here involved, two depend on the fact that all measurements of P-R express the relation between the onset of stimulation of the auricles and that of the ventricles. The first of these rests more specifically on the fact that the sinus impulse traverses the A-V junction only in the antegrade direction, whereas the A-V nodal impulse travels in part in a retrograde direction. In sinus rhythm the P-R is the sum of the time intervals occupied by the impulse while it is traveling from the auricle to the point where the A-V nodal pacemaker may arise, and from this site to the ventricles. In A-V nodal rhythm it is equal to the difference between these two intervals. The second factor depends on the fact that the sinus impulse must traverse

the auricles, in part, before reaching the region of the A-V node and passing on to stimulate the ventricles. This part of the intra-auricular conduction time is omitted in the measurement of P-R in retrograde stimulation from the A-V node (Fig. 3). This period measures 0.035 second in the dog,[28, 29] and is probably longer in the human heart. The different speed of conduction through A-V nodal tissues in antegrade and retrograde directions constitutes the third factor. In the mammalian heart it is assumed that, under normal conditions, retrograde conduction through the A-V nodal tissues is slower than antegrade conduction. This is supported by the clinical experience that R-P intervals of 0.16 to 0.19 second are more frequently observed in A-V nodal rhythm than are P-R intervals longer than 0.12 second. Of these three time factors which determine the difference between sinus and A-V nodal P-R duration, the intra-auricular conduction time is obviously independent of the site of origin of A-V nodal rhythm, whereas the influence of the other two, intrajunctional and retarded retrograde conduction, will vary according to the site of the pacemaker within the A-V nodal tissues.

Fig. 2, *A* requires special consideration. If one assumes that the site of impulse formation is the same as that in Fig. 2, *B*, the R-P interval must be explained by a shift of the block to a location above this site; or, if block existed both above and below the nodal pacemaker, the one above has now become dominant. The prolonged QRS must be explained by the existence of an additional region of block in the path to one of the bundle branch systems. There is an alternative and simpler explanation for Fig. 2, *A*, namely, that the pacemaker has shifted to a region below the bifurcation of the common bundle, with consequent aberrant spread to the ventricles and retrograde conduction to the auricles. The R-P interval in Fig. 2, *A* measures 0.16 second, and would correspond at most to a P-R of 0.20 second in the case of sinus rhythm, if correction is made for the intra-auricular time factor (but not for slower retrograde conduction).

A-V nodal rhythm with A-V block can be diagnosed when P-R is greater than plus 0.12 or minus 0.19* second and the characteristic retrograde P-wave pattern is present. It does not follow, however, that A-V block is absent when P-R intervals between plus 0.12 and minus 0.19 second are found, for it is quite possible that block may exist above and below the A-V nodal pacemaker without either one predominating (Fig. 3), or that the site of block and the site of impulse formation are such as to neutralize each other in their effect upon the resultant P-R interval.

*These figures for the limits of P-R in A-V nodal rhythm, beyond which A-V block must be assumed to be present, may not be accurate. Their precise values could be established if it were possible to ascertain (a) the shortest time for retrograde conduction when the impulse originates in the uppermost region of the A-V node, (b) the shortest time for antegrade conduction when the impulse originates in the lowermost portion of the A-V node, and (c) the normal retardation of retrograde conduction when the impulse originates in the lowermost portion of the A-V node.

SUMMARY AND CONCLUSIONS

1. A case is presented in which electrocardiograms that were taken over a period of seven months showed evidence of impaired A-V conduction. Comparison of records showing sinus rhythm with records showing a rhythm with retrograde P waves and a P-R longer than 0.12 second led to the diagnosis of A-V nodal rhythm with A-V block.

2. The effect of first degree A-V block on a rhythm originating in the A-V node is discussed. It is pointed out that the position of P with respect to QRS in A-V nodal rhythm is determined by two factors, namely, (a) the site of impulse formation in the A-V node, and (b) the speed of impulse conduction above and below the pacemaker.

3. The classification of A-V nodal rhythm as upper, middle, and lower nodal rhythm is not applicable in the presence of A-V block. Depression above the nodal pacemaker (retrograde block) will shorten the P-R interval and tend to convert it into an R-P interval; depression below the nodal pacemaker (antegrade block) will prolong P-R and tend to convert an R-P into a P-R interval.

4. The pattern of retrograde conduction (deeply inverted P_2 and P_3, with small P_1) appears to be sufficiently characteristic to warrant a diagnosis of A-V nodal rhythm even when the P-R interval is longer than 0.12 second.

5. Corrections must be made for intra-auricular conduction time and for retarded retrograde conduction in comparing the P-R of sinus rhythm with the P-R (R-P) of nodal or idioventricular rhythm; and, in nodal rhythm, corrections must be made for a third time factor, allowing for impulse spread in both directions before inscription of P or QRS.

6. In the presence of the pattern of retrograde conduction to the auricles, a P-R over 0.12 or an R-P over 0.19 second indicates A-V block; however, a P-R or R-P of shorter duration does not necessarily indicate absence of A-V block. Thus, localization of the pacemaker to a distinct portion of the A-V node based on the relationship of P to QRS may be fallacious.

7. The above conclusions regarding rhythms originating in the A-V nodal or ventricular tissues are also applicable to single beats originating in these same sites.

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ATYPICAL COARCTATION OF THE AORTA, WITH ABSENCE OF THE LEFT RADIAL PULSE

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"SO MUCH has been said and written about coarctation of the aorta, that new records of cases can have little value unless they reveal new features of interest and importance to the study of the condition." With these words, Sir Thomas Lewis began his excellent article about coarctation, in 1933.[1] The clinical picture of this congenital abnormality has become well known, so that its diagnosis is made rather frequently during life.[2-4]

Anatomically, coarctation consists of a narrowing, stenosis, or complete atresia of the isthmus of the aorta, usually beyond the origin of the subclavian artery and involving its orifice, but sometimes situated proximal to its origin. Coarctation usually does not occur as a very localized narrowing of the aorta. Ordinarily, the wall is involved to an extent of 1 to 3 inches, or even more.

The clinical picture depends upon the degree of the obstruction of the thoracic aorta and the development of compensatory collateral circulation. It follows that the signs are vascular, rather than cardiac. Retardation, with diminution or absence, of pulsation in the femoral artery, a lowered blood pressure in the lower extremities, and hypertension in the upper part of the body are the most important diagnostic signs of coarctation. These abnormalities are pathognomonic when they occur in combination with tortuous, dilated, pulsating vessels in the neck and thorax. Frequently, but not always, scalloping of the ribs is present as a result of pressure by the dilated intercostal arteries. When the diagnosis is considered, it can be established easily. When there is no discrepancy in the blood pressures in the upper and lower extremities and the femoral pulse is not diminished, the diagnosis becomes difficult, if not impossible, unless special methods of examination are employed.

We present three cases of anatomic coarctation of the aorta in which the symptomatology differed so considerably from the common type that it is described as atypical coarctation of the aorta.

CASE 1 (M. M., 472489).—This was the first admission of this 18-year-old schoolgirl to the First Medical Service of the Mount Sinai Hospital. In the preceding four years there had been twelve admissions to another hospital for what was thought to be atypical tuberculosis of the spine.

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Received for publication March 20, 1943.
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Her cardiovascular abnormalities were discovered incidentally. Six months prior to this admission, absence of arterial pulsations in the left arm was noted. The blood pressure was reported to be 164/86 in the right arm and 110/70 in the left arm.

Fig. 1.—Case 1. M. M., female, aged 18 years.
The conventional roentgenogram shows slight enlargement and rounding of the left ventricle.

The report of the clinical observations will be limited to the cardiovascular system. A systolic murmur was heard over the precordium; it extended to the left infraclavicular area and posteriorly to the left of the spine. *Pulsations of the intercostal arteries, accompanied by a thrill,* were felt over the back, particularly over the second, third, and fourth intercostal spaces to the left. A faint radial pulse was palpable on the left side. No axillary or brachial pulsations could be felt. A thrill could be felt over the left carotid artery, but not over the right. The right radial, and both femoral, pulses were normal.

By oscillometric means, the blood pressure was found to be 164/82 in the right, and 120/85 in the left, arm. The blood pressure in the legs was 174/104. While under observation the patient had several attacks

of severe headache, nausea, and vomiting, during which the blood pressure was found to be 220/110. Oscillometric readings were normal in the right arm and both legs, whereas the maximum in the left arm was found to be 0.5 (Boulitte apparatus). The electrocardiogram showed left axis deviation. The phonocardiogram revealed a late systolic murmur over the aortic and pulmonic areas, and posteriorly to the left of the spine.

Fig. 2.—Case 1.
Angiocardiogram, left lateral. In comparison with the ascending aorta, the descending aorta is hypoplastic throughout. Slight, but distinct, narrowing of the aorta just distal to the arch (white arrow). The innominate and left common carotid are well shown, but the left subclavian is not visualized at all. The left internal mammary artery is visible (black arrow), and appears to be slightly dilated and tortuous.

Polygraphic tracings revealed the following: The time relationship of simultaneous right radial and femoral pulse tracings was normal. The left radial pulse showed a slow rise, reaching its maximum in 0.22 second. The configuration of the femoral pulse tracing was normal, whereas that of the left carotid artery revealed an anacrotic notch.

A conventional roentgenogram showed slight enlargement of the heart to the left, but no other abnormality. Angiocardiographic examination showed that, as compared with the ascending aorta, the descending aorta had a small caliber, with a maximum diameter of 1.3 cm. in the thorax, or even less (1 cm.) in its abdominal portion. There was slight, but distinct, narrowing of the aortic lumen just distal to the arch; this

extended for about 3 cm. Although the innominate and left common carotid artery were well demonstrated, the left subclavian artery was not visualized, and presumably was absent.

CASE 2 (B. D., 483259).—This was the first admission of this 28-year-old woman to the Second Medical Service of the Mount Sinai Hospital. Shortly after childbirth, nine months earlier, she developed symptoms of cholelithiasis. The blood pressure in the right arm was 120/50, but it could not be measured in the left arm. Neither the left axillary, brachial, nor radial pulses could be felt. The arm, however, was warm and showed no atrophic changes. It appeared perfectly normal, and had never given rise to any complaints. The blood pressure in the legs was 170/70. No evidence of collateral circulation over the back or in the intercostal spaces could be demonstrated.

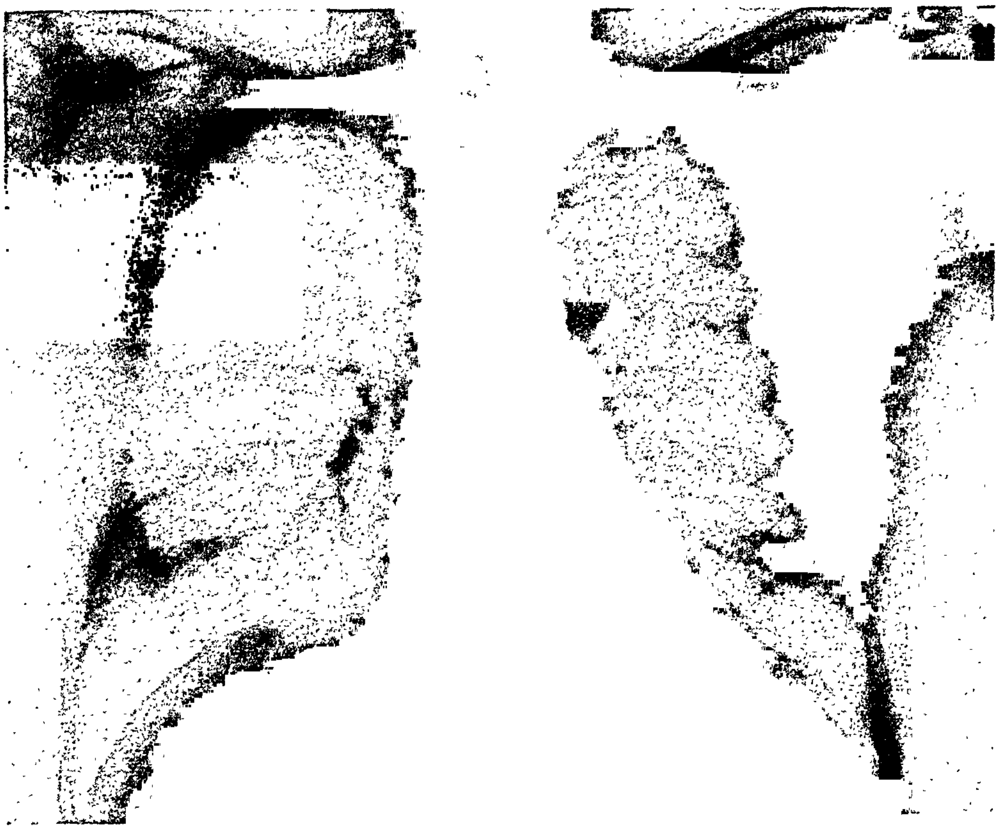

Fig. 3.—Case 3. B. P., male, aged 31 years.
The conventional roentgenogram shows no abnormality other than what appeared to be several nodular dilatations of the descending aorta (not visible in the reproduction).

The electrocardiogram revealed no abnormality.

A phonocardiogram revealed the following: There was a systolic murmur over the aortic area. Only a faint systolic murmur was recorded over the right subclavian and right carotid arteries, and there was a late systolic murmur of high frequency and of very high amplitude over the left carotid artery.

Polygraphic tracings revealed that the peak of the right carotid pulse was reached in 0.09 to 0.10 second (normal), whereas that of the left carotid pulse was reached in 0.14 to 0.16 second ("stenotic pulse"). The left radial pulse tracing was of very low amplitude, and showed a

slow rise, reaching its peak in 0.24 to 0.26 second. The relationship between the right radial and the femoral pulses was normal, i.e., the rise of the femoral pulse preceded that of the radial pulses.

The conventional roentgenogram revealed no abnormality.

Angiocardiographic examination showed an aorta of normal caliber, with suggestive, but not entirely definite, narrowing at the isthmus. Although the innominate and left common carotid artery were well visualized, the left subclavian artery could not be seen, and presumably was absent.

Fig. 4.—Case 3.

Angiocardiogram, left lateral. The aorta is irregular in outline. At the isthmus and slightly beyond the arch are two points of slight constriction of the aorta. The innominate and left common carotid artery are well visualized and do not appear grossly abnormal. The left subclavian artery is occluded about 1 cm. from its origin (white arrow). The left internal mammary artery is moderately tortuous and dilated (black arrow).

Case 3 (B. P., 490179).—This was the first admission of this 31-year-old soda clerk to the First Medical Service of the Mount Sinai Hospital. The complaint for which he sought admission was numbness and tingling in the left upper extremity, which had been present for about six years. These symptoms occurred most often after exercise, and subsided after rest. About one year before admission he had an attack of severe, crush-

ing, parasternal pain which lasted several hours; this was thought by his physician to be caused by acute coronary thrombosis. The electrocardiogram at that time showed a notched QRS_3 and an inverted T_3. The patient was kept in bed for three months. He was then well except for cramps, numbness, and blanching of the left arm after exercise. During the week before admission he experienced dull aching pain over the left side of the chest and left arm. There was no history of orthopnea, dyspnea, or edema.

Examination showed that the patient was of muscular build and did not appear ill. The abnormal signs were limited to the vascular system.

By percussion, the heart appeared to be somewhat enlarged. There was a rough systolic murmur over the aortic area, which appeared even louder over the right subclavian, right carotid, and left carotid arteries. Only a flicker of pulsation could be felt in the left subclavian, axillary, brachial, and radial arteries, and the blood pressure could not be obtained in the left arm by the auscultatory method. By the oscillometric method it was found to be about 130/90. In the right arm the blood pressure was 180/88. The pulses of the lower extremities were all normal, and the blood pressure was about 210/110 by the oscillometric method. No evidence of collateral circulation could be found over the back in the intercostal spaces.

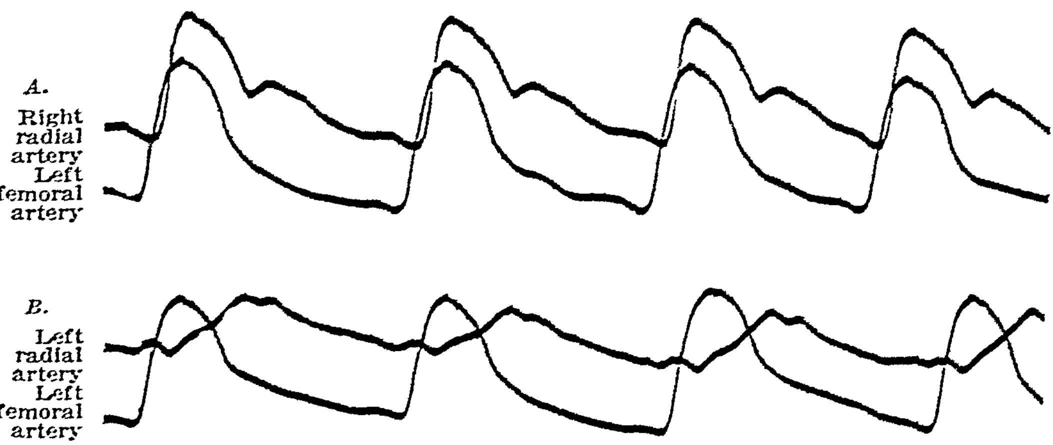

Fig. 5.—Case 3.
Simultaneous radial and femoral arterial pulse tracings.

A, The relationship between the right radial and the femoral is normal, i.e., the rise of the femoral pulse precedes that of the radial pulse. The configuration of the pulses is normal.

B, The left radial pulse has a very slow rise. Its relationship to the femoral pulse is normal, as is that of the right radial artery.

The electrocardiogram revealed no abnormality.

A phonocardiogram revealed the following: There was a systolic murmur of high amplitude over the right subclavian, right carotid, and left carotid arteries. No murmurs could be recorded over the spine.

Pulse tracings taken over the left carotid artery revealed an anacrotic notch and a few vibrations in the systolic portion. The left radial pulse had a very slow rise, reaching its maximum after 0.28 second. The relationship between the right radial and the femoral pulses was normal, i.e., the rise of the femoral pulse preceded that of the radial pulse.

A conventional roentgenogram of the chest showed no abnormality other than what appeared to be several nodular dilatations of the descending aorta. Angiocardiographic examination showed that the

aorta had an irregular outline, although no aneurysm was present. At the isthmus and several inches beyond the arch, there were two points of slight constriction of the aorta, suggesting mild coarctation. The innominate artery and its branches and the left common carotid artery were well visualized and did not seem grossly abnormal. The left subclavian artery, however, was occluded about 1 cm. from its origin.

DISCUSSION

The common features of these three cases are summarized as follows:

All of them showed anatomically a relatively extensive involvement of the aorta at the isthmus and the distal portion of the arch, causing a slight narrowing. However, there was no obstruction to the blood flow in the thoracic aorta. This explains the fact that the relationship of the blood pressure in the lower, to that in the upper, extremities was normal, and that the pulse wave in the femoral artery was not retarded. However, in all three cases the orifice of the left subclavian artery was obstructed, resulting in almost complete absence of the left radial pulse. The origin of the left common carotid artery presumably, also, was narrowed, for there was a stenotic pulse, as well as a systolic murmur and thrill. In the third case even the orifice of the innominate artery seemed to be involved. The aorta in the first case was hypoplastic beyond the isthmus; the same patient also showed collateral circulation.

Hypertension was present in two cases. Two possible mechanisms have been suggested. By some, the hypertension is thought to be caused by renal ischemia, as suggested by the experimental work of Goldblatt.[5] Hypertension has been produced by several workers by clamping the aorta at various levels. A mechanical cause for the hypertension is suggested by Maycock's case.[6] Here the stenosis was below the origin of the renal arteries, yet there was a blood pressure of 220/80 in the arm. The presence of an elevated diastolic pressure in the lower extremities, which is found in only about half of the cases,[7] is not necessarily an expression of the general distribution of peripheral resistance,[8] for it may well represent a compensatory mechanism similar to that encountered occasionally in aortic stenosis when a high diastolic pressure is present. Erosion of the ribs was not present in any of the cases.

In contrast to typical coarctation, there was no discrepancy between the blood pressures in the lower and upper extremities, no diminution of the femoral pulsations, and no retardation of the pulse wave in the lower extremities.

There is no report in the literature of a case in which the clinical diagnosis has been made in the presence of the abnormalities described above. Pathologically, three similar cases have been reported, two by Fawcett[9] from the old records of Guy's Hospital, which showed a slight ridge at the isthmus (Cases 14 and 16). The third case, reported by Binder,[10] in 1919, almost duplicates the conditions in our first case. In

his case the circumference of the ascending aorta was given as 6 cm., that of the distal portion of the arch as 3.4, the isthmus as 3.1, and the descending aorta as 3.4 cm. At the isthmus the lumen was slightly irregular, especially in the region of the insertion of the ligamentum arteriosum of Botallo. The initial portion of the cervical vessels was remarkably stiff, thickened, and slightly narrowed. Involvement of the whole arch of the aorta has been recently reported by Franke[11] in a case of typical coarctation.

CONCLUSION

A hitherto undescribed syndrome of atypical coarctation of the aorta, with absence of the left radial pulse, is discussed. Its presence may be suspected by clinical and polygraphic examinations, but can be proved only by angiocardiographic examination.

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ELECTROCARDIOGRAPHIC STUDIES AFTER SURGICAL OPERATIONS ON THE HEART

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THE present observations concern the evolution of the electrocardiograms of patients who were subjected to cardiac operations by Dr. Claude S. Beck. This paper supplements a previous report[1] of observations made during cardiac operations by the same surgeon. The operations were of two types: (1) operations for chronic cardiac compression (24 cases), and (2) operations for coronary artery sclerosis (21 cases).

The predominant electrocardiographic abnormalities during the operations for chronic cardiac compression were ventricular premature beats, ventricular tachycardia, and, occasionally, RS-T deviations; during the operations for coronary artery disease, isolated ventricular beats, ventricular tachycardia, and deviations of the RS-T segment were of frequent occurrence. Stewart and Bailey[2] reported electrocardiographic studies during the course of pericardiectomy in six cases. Their observations were similar to ours except that auricular tachycardia, auricular fibrillation, and auricular flutter occurred in one of their cases, and ventricular fibrillation, nodal rhythm, and shifting pacemaker were not noted in their series. Changes in the RS-T interval were not present to any significant degree in their cases. Serial electrocardiograms which were taken for months after operation showed surprisingly few changes in the form of the T waves and RS-T segments in their cases.

STUDIES AFTER OPERATION FOR CHRONIC CARDIAC COMPRESSION

Twenty-four cases were observed from fourteen days to seven years after the operation (Table I). Regular sinus rhythm was present in sixteen cases throughout the period of observation; persistent auricular fibrillation was present in five cases; auricular flutter was seen in two patients, and, in one, auricular flutter was followed by persistent auricular fibrillation. Efforts to convert auricular fibrillation to normal rhythm were ineffectual. Ventricular premature beats occurred occasionally in ten cases, usually during the early postoperative course. Auricular premature beats were observed in one case early in convalescence. The following case is illustrative of this group:

L. G., a white man, aged 43 years, presented the typical clinical picture of chronic cardiac compression. He was cyanotic and the superficial

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Received for publication March 24, 1943.

TABLE I

CHRONIC CARDIAC COMPRESSION

CASE NO.	RHYTHM	AURICULAR PREMATURE BEATS	VENTRICULAR PREMATURE BEATS	AURICULAR FIBRILLATION	AURICULAR FLUTTER	LENGTH OF OBERVATION YR.	MO.	DAYS
1.	Normal					1	8	
2.	Normal					2	6	
3.			2 mo. postoperative	Pre- and postoperative			2	
4.			2nd and 3rd year	Pre- and postoperative		6	3	
5.	Normal					1	1	
6.	Normal		1st and 2nd month				2	15
7.	Normal							18
8.	Normal		3 months				3	
9.	Normal							14
10.	Normal							19
11.	Normal		Immediately postoperative			1	4	
12.	Normal					2		
13.	Normal	6 mo.					6	
14.			Immediately postoperative	Pre- and postoperative			9	
15.	Normal						1	
16.			Continuous 2nd week on	Pre- and postoperative			1	
17.	Normal				4 months		5	
18.	Normal						1	
19.				3rd week on	Pre- and postoperative to 3rd day		10	
20.			2 yr., 6 mo.	Pre- and postoperative		3	8	
21.			2nd day		1 yr., 8 mo.	1	8	
22.	Normal		4 months			3	10	
23.	Normal						2	
24.	Normal	Wandering pacemaker pre- and postoperative Normal mechanism two months later				1	3	

veins were distended. There were pleural effusion and ascites; the liver was considerably enlarged. The heart was not enlarged, there was no palpable precordial activity, and the heart sounds were feebly heard. Pericardiectomy was successfully performed and the convalescence was uneventful. He was followed for a period of two years, during which period he was able to return to his work. His electrocardiograms (Fig. 1) illustrate the typical electrocardiographic pattern in this group of cases.

A, Taken postoperatively, shows moderately low voltage of QRS and inversion of T in Leads II, III, and IVR.

B, Taken twenty-four hours postoperatively, shows increased right axis deviation and a slight increase in amplitude.

C, Taken almost ten months after operation, shows increased amplitude of QRS.

D, Taken one year and eight months after operation, shows normal amplitude of QRS, slight inversion of T in Leads I and II, and a sharply negative T in Lead IVR.

The chief change in this record is the increase in the amplitude of all complexes and slight variations in T. These changes are similar to those in a previous report concerning the electrocardiographic changes in cases of cardiac compression.[3]

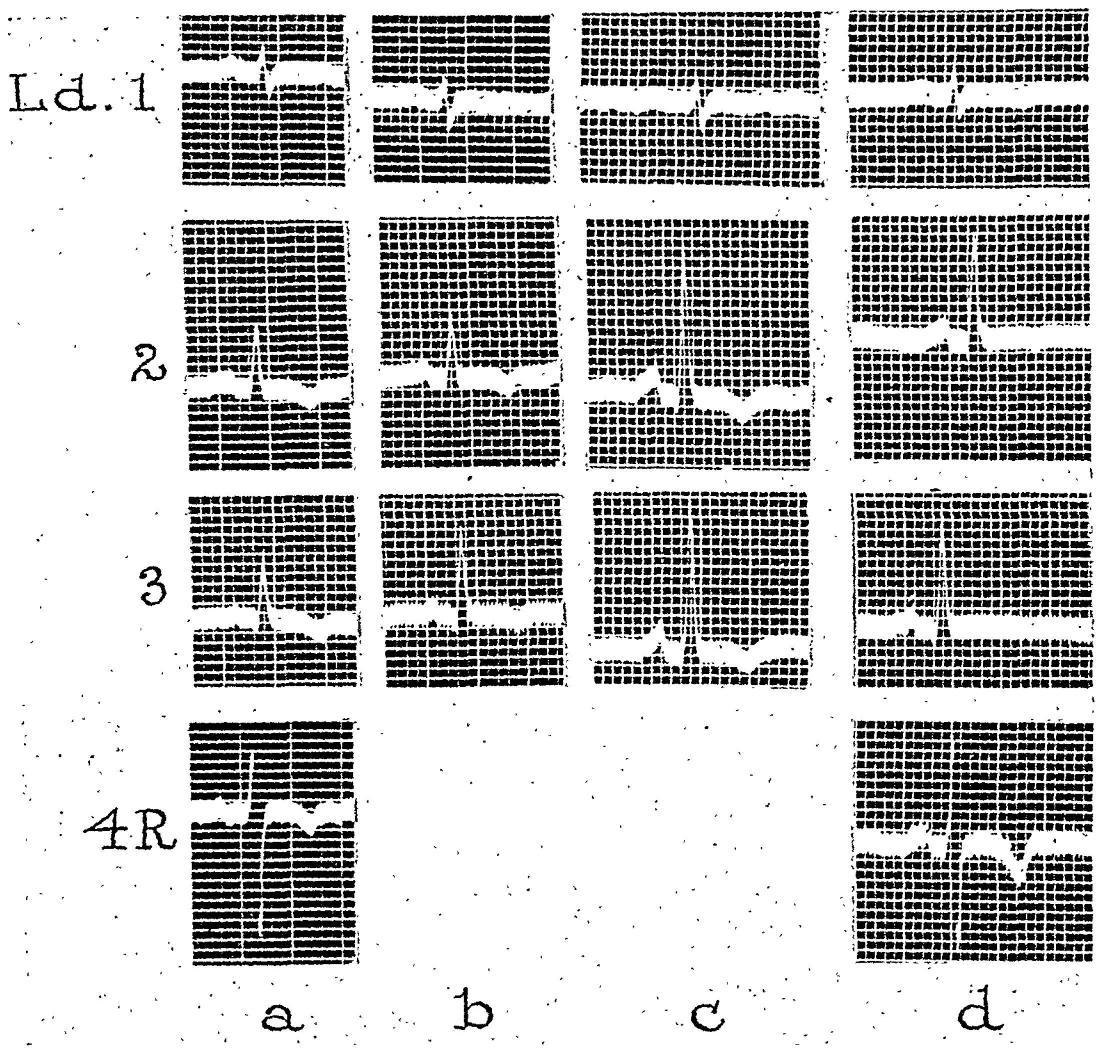


Fig. 1.

There were eight cases in which there were slight changes in the RS-T segment, and these occurred at varying times during the postoperative period. These observations are summarized in Table II.

The preoperative low amplitude of the electrocardiogram (Table III) is probably due to a number of factors: (a) atrophy of cardiac muscle caused by the chronic cardiac compression and the reduced coronary artery flow, the result of reduced cardiac output; (b) the insulating effect of the scar;[4] and (c) the accumulation of fluid in the body cavities and the increase in extracellular fluid. Roberts and Beck[5] showed that the cardiac muscle fibers were smaller than normal as a

TABLE II

CHRONIC CARDIAC COMPRESSION; CHANGES IN RS-T SEGMENTS

CASE NO.	RS-T CHANGES	LIMB LEADS	TIME OF OCCURRENCE
5.	Slight elevation	Lead III	1 yr., 1 mo. postoperative
7.	Slight depression	Leads I and III	Preoperative
	Slight elevation	Leads I and II	Immediately postoperative
	Slight elevation	Lead I	1 day postoperative
	Isoelectric	All leads	2nd day on
8.	Slight elevation	Lead I	2nd day postoperative
	Slight depression	Lead III	2nd day postoperative
	Slight depression	Lead III	2 weeks postoperative on
	Slight depression	Lead I	3 weeks on
10.	Slight elevation	Leads II and III	6 months
15.	Slight depression	Leads I and II	Immediately postoperative
	Isoelectric	All leads	1 week later
	Slight depression	All leads	1 month
19.	Slight depression	All leads	Immediately postoperative
20.	Slight depression	Leads II and III	Immediately postoperative
	Isoelectric	Leads II and III	1 year
	Slight depression	Leads II and III	2 years
24.	Slight depression	Lead I	Immediately postoperative

TABLE III

CHRONIC CARDIAC COMPRESSION (VOLTAGE)

LOW BEFORE OPERATION	RETURN TO NORMAL AFTER OPERATION	LOW AFTER OPERATION	NO CHANGE	NORMAL BEFORE OPERATION	INCREASE AFTER OPERATION (NORMAL BEFORE OPERATION)
LIMB LEADS					
20 (57.1%)	12 (60.0%)	8 (40.0%)	7 (46.7%)	15 (42.9%)	8 (53.3%)
CHEST LEADS					
16 (45.7%)	13 (81.2%)	3 (18.8%)	9 (47.9%)	19 (54.3%)	10 (52.1%)

result of chronic cardiac compression in both experimental and clinical cases. On the other hand, Katz, et al.,[6] reported the electrocardiographic observations in three cases of brown atrophy of the heart. In all cases there were left axis deviation and normal amplitude of the complexes. There was usually some immediate postoperative increase in the amplitude of QRS in our cases, and this suggests that the most important factors in bringing this about are: the increase in cardiac output, the result of release of the heart from the glove-fitting compression scar; the improvement in coronary flow, the result of both increased cardiac output and release from cardiac compression; the removal of the insulating scar; and the diminution in the extracellular fluid. This increase in amplitude was usually progressive until normal values were recorded. The T-wave changes were inconstant and not uniform in the serial records (Table IV). This is in agreement with Stewart and Bailey,[2] who stated that "Serial electrocardiograms which were taken for months after operation showed surprisingly few changes in the form of the T waves and R-T segments." The dissection of the pericardial scar may be between its layers rather than between scar and myo-

cardium. This was so in one case in which an autopsy was performed five years after operation.* Considerable scar was found still remaining.

TABLE IV

CASE NO.	LEAD I	LEAD II	LEAD III	CHEST LEAD
	T Waves in Chronic Cardiac Compression (Preoperative)			
1.	+	–	sl.–	sl.–
2.	iso	iso	iso	very sl.–
3.	sl.–	sl.–	iso	–
4.	–	–	sl.–	–
5.	iso	very sl.–	iso	+
6.	+	di	sl.–	iso
7.	+	–	–	cove–
8.	sl.–	–	very sl.–	–
9.	iso	+	+	+
10.	iso	+	iso	+
11.	–	–	sl.–	–
12.	+	+	sl.–	di
13.	iso	sl.–	di	+
14.				
15.	–	–	iso	cove–
16.	iso	iso	iso	+
17.	sl.–	di	di	sl.–
18.	+	sl.–	–	+
19.	iso	+	+	+
20.	+	+	sl.–	+
21.	iso	iso	very sl.–	+
22.	iso	iso	+	sl.+
23.	+	+	–	+
24.	sl.–	sl.–	+	–
	T Waves in Chronic Cardiac Compression (Postoperative)			
1.	iso→ sl.– 2 yr.	sl.– throughout	sl.– throughout	– cove → –
2.	iso→ di→ + 4 yr.	iso→ sl.–	iso → sl.–	sl.– → cove– → –
3.	sl.–	sl.– → +	di → iso→ +	–
4.	di→ iso→ + 1 yr.	sl.– → + → sl.–	sl.– → iso→ di→ sl.–	sl.– → + → – → +
5.	iso→ di→ sl.– 1 yr.	sl.–	sl.– → di	–
6.	+ → iso→ + 1 mo.	sl.–	sl.–	sl.–
7.	+	– → sl.– → di	– → di	– → cove
8.	–	–	sl.– → di → +	+ → di→ cove→ –
9.	+ → sl.– 2 wk.	+ → very sl.–	iso → sl.+	–
10.	di→ sl.– 19 days	di → sl.–	iso → +	no record
11.	+ → di→ sl.– 1 yr.	sl.–	di → very sl.–	– → di
12.	+ → +	di	sl.–	+ → –
13.	iso → +	di → +	sl.– → di	+
14.	+	sl.– → iso	– → iso	– → +
15.	sl.– → –	di → sl. –	di → sl.– → +	–
16.	iso → sl.–	iso → sl.– → di	sl.– → di → +	cove → –
17.	di → sl.–	di → sl.–	– → sl.– → +	no record
18.	+ → + → iso	– → sl.– → +	– → di	+
19.	+ → di→ – → iso	+ → sl.–	+ → di → sl.–	no record
20.	+	sl.– → +	sl.–	– – + – di
21.	iso → iso → +	iso → iso	iso → di → –	– → di → +
22.	+ → iso → sl.– → –	iso → di → iso	iso → +	– → sl.–
23.	+ → sl.– → –	+ → sl.–	di → sl.–	–
24.	di	+ → sl.–	iso → sl.–	sl.–

– inverted
+ up
sl.– slightly inverted
di diphasic
iso isoelectric

*The pathologic examination was made by Prof. H. T. Karsner.

TABLE V

RHYTHM IN CASES OF CORONARY SCLEROSIS (POSTOPERATIVE)

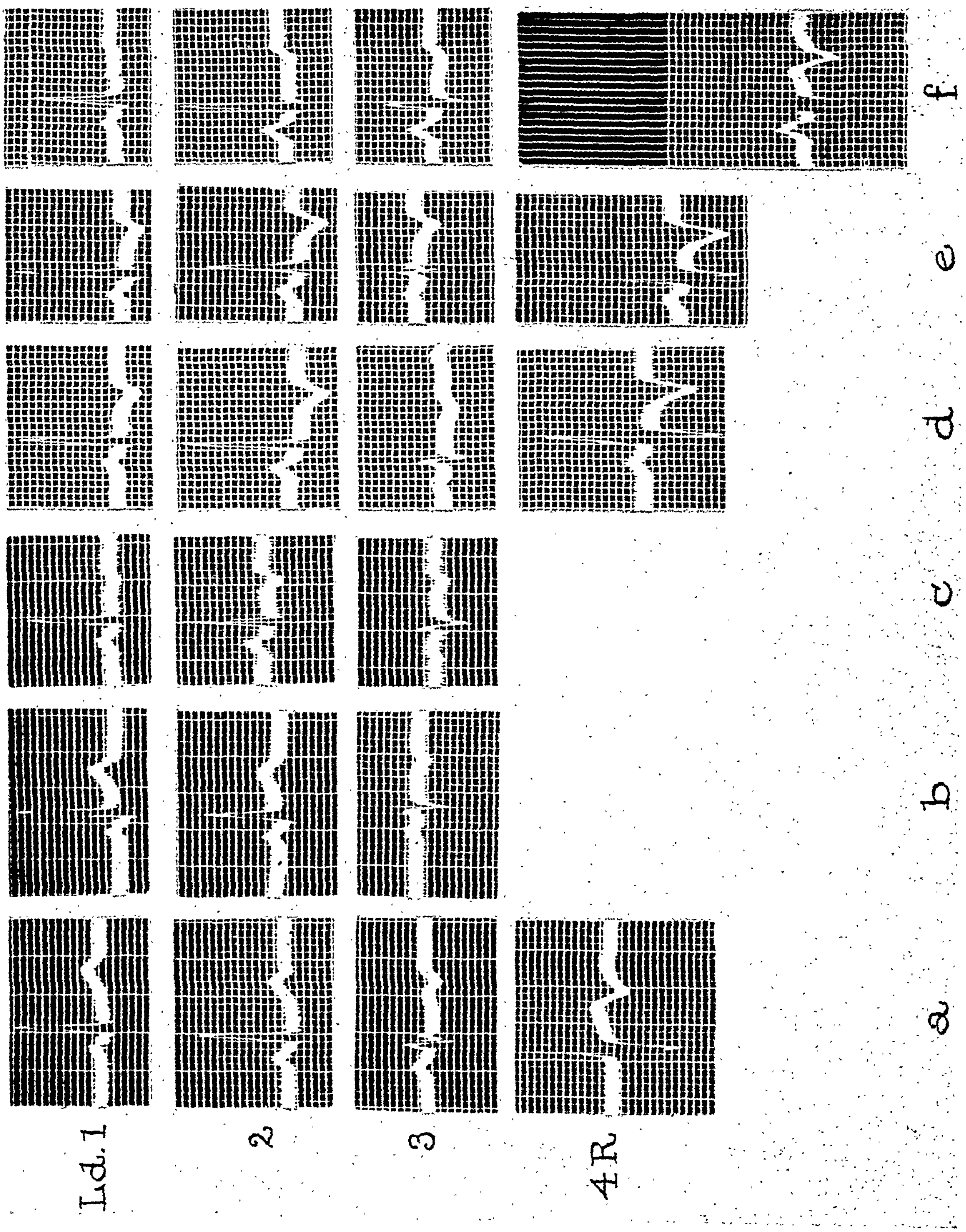
CASE NO.	REGULAR SINUS RHYTHM	AURICULAR PREMATURE BEATS	VENTRICULAR PREMATURE BEATS	AURICULAR FIBRILLATION	AURICULAR FLUTTER	LENGTH OF OBSERVATION
1.	*	-	-	-	-	5 yr., 8 mo.
2.	*	First day 1 week 2 weeks	2 weeks	-	-	6 yr., 6 mo.
3.	*	-	-	-	-	4 yr., 8 mo.
4.	*	Second day	-	First day	-	2 mo.
5.	*	-	-	-	-	2 yr., 10 mo.
6.	*	-	Sixth-twelfth day	-	-	5 yr., 9 mo.
7.	*	-	2 months	-	-	5 yr.
8.	*	-	Control and throughout	-	-	3 mo.
9.	*	-	-	-	-	2 mo.
10.	*	-	-	-	-	4 mo.
11.	*	-	-	-	-	2 yr., 1 mo.
12.	*	-	1 month	-	-	3 yr., 4 mo.
13.	*	-	-	-	-	3 yr., 2 mo.
14.	*	-	-	-	-	2 yr., 6 mo.
15.	*	-	-	Third-fifth day	-	1 yr., 3 mo.
16.	*	-	-	-	Seventh day	2 mo.
17.	*	-	1 month	-	-	2 yr., 1 mo.
18.	*	First day	-	-	-	2 mo.
19.	*	-	-	-	-	1 yr. 6 mo.
20.	*	-	Third day and 13th to 14th mo.	-	-	1 yr. 2 mo.
21.	*	-	-	-	-	5 days
22.	*	-	First day	-	-	6 yr.. 2 mo.

In this case (No. 5) there was no elevation of the RS-T segment until thirteen months after operation.

STUDIES AFTER BECK'S OPERATION FOR CORONARY ARTERY SCLEROSIS

There were twenty-two patients in this group who were followed from five days to six and one-half years. The usual pattern of the electrocardiogram consists of elevation of RS-T in all leads; this was usually greatest within three days (86.3 per cent), but was delayed as long as seven days in one case. The elevation was greatest in Lead II. The onset of the elevation was noted either immediately, or, most frequently, within the first two postoperative days (81.8 per cent). After this, the elevation receded and T became depressed, reaching its maximum depression in seventeen days (63.6 per cent), although there were three cases in which T reached its greatest depression in 42, 45, and 74 days, respectively.

In Table V the data concerning disturbances in rhythm are tabulated. In all cases the predominant rhythm was normal. Auricular premature beats occurred in three cases, ventricular premature beats in eight cases, transient auricular fibrillation in two cases, and transient auricular flutter in one case.


Ld. 1
2
3
4R
a
b
c
d
e
f

The following case is illustrative of this group:

C. Z., a white man, aged 49 years, complained of typical attacks of angina pectoris for six months; these were increasingly severe and incapacitating. Beck's operation was performed in 1937, and was followed by an uneventful recovery. The patient progressively improved, and was able to return to his work with but few anginal attacks. Five years after the operation, the patient was symptom-free. His electrocardiograms (Fig. 2) illustrate the typical electrocardiographic pattern in this group.

A, Taken preoperatively, shows a diphasic T in Lead IVR.

B, Taken two days after the operation, shows elevation of the RS-T segment in Leads I and II and inversion of T in Lead III.

C, Taken one week later, shows RS-T isoelectric and T in Leads I, II, III, and IVR inverted.

D, Eight days later, and *E*, Nine days later, show progressive increase in the amplitude of R and increasing depth of T inversion.

F, Last record, taken three years and eight months after operation, shows a still greater amplitude of QRS, isoelectric T in Lead I, and diphasic T in Leads II and III. The T wave in Lead IVR remained deeply inverted. On the second postoperative day there was slight transient left axis deviation (*B*), persisting until the ninth postoperative day. There were no changes of significance in P, P-R interval, heart rate, or rhythm.

In summary, there is elevation of the RS-T segment early in the postoperative course. This elevation rapidly subsides and T becomes progressively inverted. Finally T returns toward normal, but remains diphasic. These changes resemble those in both experimental[7] and clinical pericarditis.[8] The changes are due to the inflammatory reaction in the superficial myocardium, and are caused by the instrumental abrasion of the pericardium at the time of the operation. The changes were not due to distention of the pericardium because, at the time of operation, an incision was made in the inferior posterior surface of the parietal pericardium, allowing drainage into the pleural sinus.

SUMMARY

1. Electrocardiographic studies after twenty-four operations for chronic cardiac compression and twenty-one operations for coronary artery sclerosis are reported.

2. In cardiac compression cases there is frequently a gradual increase in the amplitude of the deflections. The T-wave changes were inconstant and not uniform in serial records.

3. Patients with coronary artery sclerosis show a constant pattern of RS-T elevation which gradually disappears and is followed by a sharp depression of T.

4. The greater electrocardiographic changes in the coronary artery sclerosis cases are probably the result of more severe damage of the superficial myocardium.

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ELECTROCARDIOGRAPHIC CHANGES IN RELATION TO TOLERANCE OF SUSTAINED ANOXEMIC ANOXIA IN DOGS

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ALTHOUGH many publications[1] deal with the effects of acute, progressive anoxia on the heart and circulation, comparatively few are concerned with the factors which determine the tolerance of more sustained anoxia. Armstrong,[2] and Armstrong and Heim[3] have given a general review, and the former has studied the tolerance of rabbits at different altitudes.[4]

The earliest and most extensive electrocardiographic studies during short periods of progressive anoxia were made by Greene and Gilbert.[5-7] They stressed particularly the disturbances of rhythm and conduction which develop at the crisis. More recently, electrocardiographic recordings made during flying[8-12] and in cardiac diseases[13-18] indicate that sustained anoxia leads to depression of the S-T segment and of the T wave, and occasionally to deformation of the QRS complex. This has led to the inference that anoxemic anoxia causes myocardial impairment, a conclusion not supported by experimental studies on animals in which progressive anoxia causes an increased vigor of ventricular beats and an augmented cardiac output.[19-21]

Since such judgments regarding the effects of anoxia on the myocardium are based on comparing results obtained by dynamic studies on anesthetized dogs with those obtained by electrocardiographic studies on man, it seemed important to make additional electrocardiographic observations on such dogs. It is conceivable that species differences exist; also, that the dynamic effects reported during acute progressive anoxia do not apply during sustained anoxia.

This report deals with the electrocardiographic changes, correlated with respiratory and circulatory responses of dogs, during prolonged exposure to various reduced percentages of oxygen. The rebreathing method was used in order to ascertain the influence of anoxemic anoxia, separate from additional influences of temperature and pressure changes such as occur in ascent to higher altitudes.

METHODS AND APPARATUS

The dogs were anesthetized with a small preanesthetic dose of morphine and sodium barbital (175 mg. per kilogram), and placed upon a heated

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This investigation was aided by a grant from the John and Mary R. Markle Foundation.

Received for publication March 27, 1943.

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animal board. In order to maintain reflexes arising from the carotid sinus areas, mean blood pressure was recorded from the femoral artery by means of a mercury manometer. Leads I, II, III, and sometimes IV were recorded by a Sanborn electrocardiograph at 50 mm. per second. Tracheotomy was performed, and the dog was connected directly to a recording segment respirometer. This apparatus, originally designed by Burlage and Wiggers[23] for studying the effect of hypercapnia, and modified to study the effects of anoxia, has been used for many years in this laboratory for both animals and man. Since the modifications which permit one to vary the rate of reduction in percentage of oxygen breathed (theoretical rate of ascent) and to maintain the ultimate reduced percentage of oxygen breathed (attained theoretical altitude) have not hitherto been described, a brief description of this cheap and efficient rebreather is incorporated.

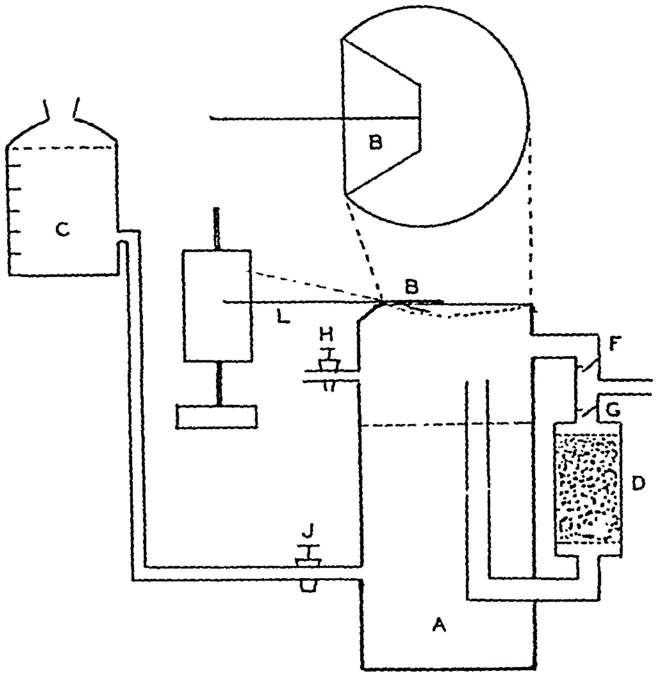

Fig. 1.—Diagram of segment respirometer for study of effects of anoxia.

As shown diagrammatically in Fig. 1, the segment respirometer consists of a metal ash can (*A*), the top of which has been somewhat extended and shaped as a large segment capsule (see surface view, Fig. 1). It has a capacity of 80 liters, which is suitable for human tests, but this can be reduced by partial filling with water to any capacity (e.g., 25 liters is suitable for 10 kilogram dogs). The top is covered with a sheet of light rubber dam, and to this is cemented a trapezoidal piece of stiff cardboard (*B*) which, with its long straw pointer, pivots on the segment side of the rubber. As the rubber membrane is drawn in during inspiration, the lever rises, and vice versa during expiration. The apparatus is easily calibrated by allowing known volumes of water to run into the tank from a 5 gallon graduated bottle (*C*). In this way, changes in respiratory rate, as well as in the total and minute volumes, are quantitatively recorded throughout the experiment.

To the tank is connected a canister of soda lime (*D*). When a subject or animal is connected to the apparatus at *E*, air from the tank is inspired via valve *F* and returned to the spirometer through the soda lime (*D*) via valve *G*. As CO_2 is thus removed and oxygen is consumed,

the rubber membrane tends to draw into the tank and the recording lever rises. To prevent this, a stream of water is permitted to flow from a bottle (*C*), at such a rate that the membrane and lever remain horizontal during expiration. Since the air in the spirometer is practically saturated with water, the rate at which water is admitted equals the rate of oxygen consumption. Knowing the air volume above the water, computations of the percentage reduction of oxygen in the respirometer for each liter or half-liter of water admitted can easily be made. This agrees well with actual determinations of the volume percentages of oxygen made by gas analysis, which were used as checks in these experiments. When the volume per cent of oxygen has been reduced to a desired level, say 10 or 12 volumes per cent, the flow of water is stopped, and, in its place, a continuous stream of oxygen from a tank equipped with a needle valve is admitted via a stopcock (*H*).

A little consideration makes it obvious that the rate of oxygen reduction after connection to an animal depends on the relation between the effective air capacity of the tank and the rate of oxygen consumption, which, among other factors, depends on the size of the dog and its metabolic rate. However, by merely changing the starting air capacity of the respirometer, the rate of oxygen reduction of the inspired air (i.e., the simulated rate of ascent to high altitudes) can be altered; the smaller the respirometer volume, the more rapid the oxygen reduction and the simulated rate of ascent. In these experiments, simulated ascension varied from 250 to 880 feet per minute, but a rate of about 400 feet per minute was most commonly employed. Exposures varied from twenty minutes at 11 per cent (ca. 17,000 feet altitude) to seven and one-half hours at 7 per cent (ca. 27,000 feet altitude) oxygen.

RESULTS

Twenty-two dogs were used in these experiments. The starting heart rates were more rapid than normal as a result of the barbital anesthesia. This is not a disadvantage, for it eliminates the possibility of changing the configuration of the electrocardiogram by increased rates, and essentially reduplicates an emotional cardiac acceleration, such as may occur prior to "taking off" in an airplane.

Since the main objective of the study was to investigate the changes which occur during sustained anoxia, only a brief outline of the responses during the period of simulated ascent will be described. Heart rate and mean pressure were generally unaffected, although the latter sometimes increased a trifle. Respiratory rate and minute volume augmented, as has often been noted (Figs. 2 and 4). Electrocardiographic changes were not prominent during this period, and no essential differences were noted when the rate of oxygen reduction (rate of ascent) was varied within the ranges stated above. Nor did the altitude reached produce any effects. The responses to sustained anoxia were generally the same in all the animals, but considerable individual variation was noted in the ability to withstand low oxygen mixtures. One animal failed after three and one-half hours at 13 per cent oxygen (12,500 feet), another after twenty minutes at 11 per cent (17,000 feet), and still another after three hours at 4.5 to 5 per cent (38,000 to 40,000

feet). In general, 7 to 8 per cent (25,000 to 27,000 feet) was found to be the critical level at which all animals failed after several hours of exposure. Dogs, like human beings, can be placed, therefore, in one of two broad groups: those which tolerate low oxygen mixtures well, and those which do not. In order to best illustrate the typical responses of "tolerant" and "nontolerant" dogs, together with certain variations, an experiment of each type will be described in detail.

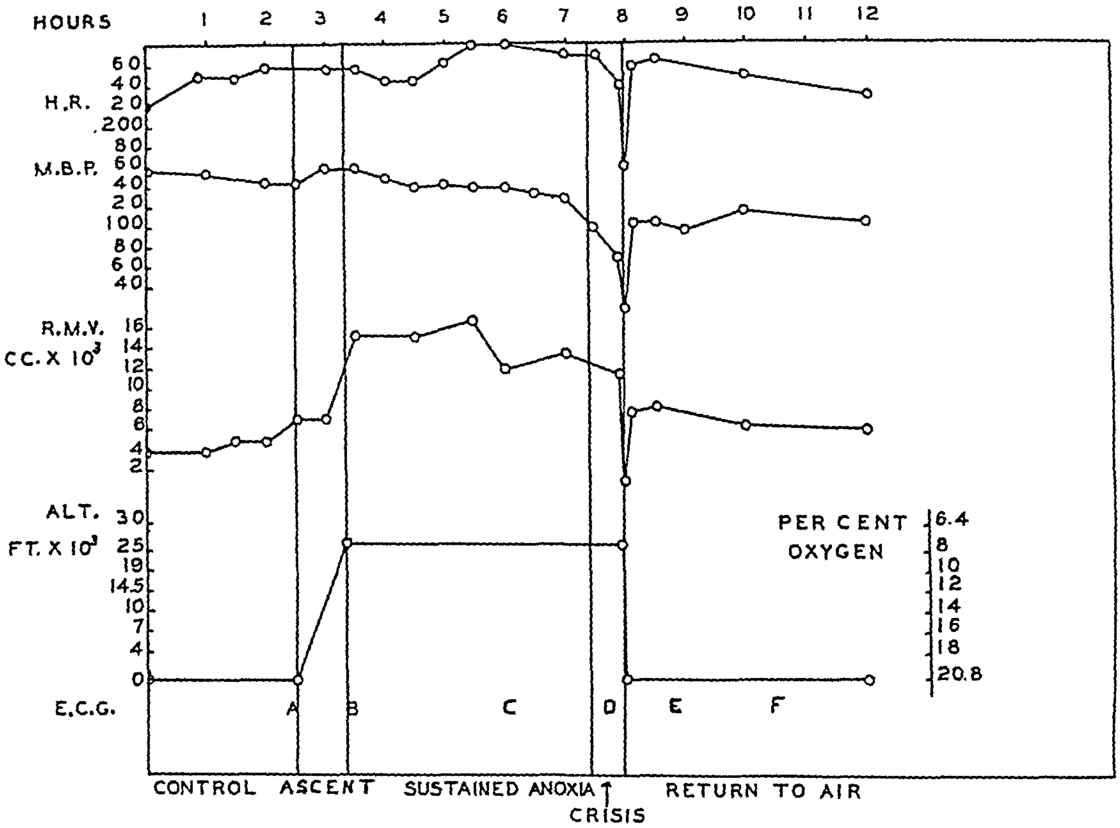

Fig. 2.—Responses of a normal, tolerant dog to sustained anoxia. *H.R.* refers to heart rate; *M.B.P.*, to mean blood pressure; *R.M.V.*, to respiratory minute volume in cubic centimeters; *ALT.* to altitude in feet; and *E.C.G.* to electrocardiogram. Segments of electrocardiograms were selected from a continuous series taken throughout the experiment, and refer to similar lettering in Fig. 3. Oxygen percentages equivalent to altitude are charted at the right of the figure.

Fig. 2 illustrates the reactions of an animal of the more tolerant group (No. 14) when the volume per cent of oxygen was decreased to 7 per cent in forty-five minutes (a simulated ascension to about 27,000 feet at a rate of 600 feet per minute). The animal remained at this altitude for four hours and forty minutes. During the later stages of the simulated ascent, both respiratory rate and amplitude were greatly increased, and the minute volume reached four times that of the control period. This was maintained for about two hours at the peak altitude, and then decreased to a volume three times the normal until the crisis. At this time the hyperpnea was suddenly replaced by very slow, irregular breathing which lasted but a few minutes, followed by apnea. Immediate institution of artificial respiration and return to atmospheric air was marked by resumption of an essentially normal minute volume of respiration.

After an initial rise during rebreathing, the mean blood pressure gradually fell to, and remained at, essentially normal levels for two hours and forty minutes. After this time, a progressive and rapid fall in pressure proceeded abruptly into the period of crisis, when complete failure of both circulation and respiration resulted. It is difficult to say which function fails first, but it is generally noted that, after the blood pressure reaches levels of 50 to 70 mm. Hg, complete circulatory failure is precipitated by respiratory collapse. The heart rate was abnormally rapid during the control period, but, even so, showed a further significant acceleration during the period of anoxia. The rate remained very rapid until a precipitous fall occurred during the crisis which marked the circulatory failure. It appears, therefore, that the respiratory center remains viable until the blood pressure has fallen to about 50 to 70 mm. Hg. At this time an insufficient amount of oxygen is apparently supplied to the medullary respiratory centers, with consequent failure and death unless artificial respiration is instituted at once. When this dog was given temporary artificial respiration and returned to atmospheric air, the mean blood pressure returned to 105 mm. Hg, and remained at this level for several hours. However, after eight hours, the arterial pressures gradually fell, and the dog died about fourteen hours after this partial recovery from the period of crisis.

Segments of the electrocardiograms taken at intervals indicated in Fig. 2 as *A*, *B*, *C*, etc., illustrate the progressive responses during sustained anoxia. Segment *A* (Fig. 3) is a normal control, and *B* shows a depression of 2 to 3 mm. in the QRS complex in all leads at the end of the period of ascension. This depression of QRS continued and became progressively more severe with continued exposure to low oxygen tensions, especially in Leads II and III (Fig. 3, *C*). Extreme depression and definite splintering were apparent in Lead III two hours and forty minutes after reaching the peak altitude (Fig. 3, *D*), and persisted in modified form throughout the experiment. Changes were less striking and less consistent in Lead II.

The P-R interval decreased about 10 millisecond during the early acceleration in heart rate, and failed to increase even when the heart slowed during the crisis. In those experiments in which ultimate cardiac depression supervened, a lengthened P-R interval, as described by Greene and Gilbert,[5-7] was observed. The duration of the QRS, as measured by the width of the R, decreased early by about 5 millisecond and remained so. The total duration of electrical systole (Q-T interval) also decreased with the total cycle time, and failed to become elongated until frank cardiac failure supervened.

The S-T segment and T wave were not significantly altered throughout this experiment, except for a tendency toward the development of a diphasic T wave in Lead I just prior to failure (Fig. 3, *D*). No evidence of a depression of the S-T segment was seen at any time.

When the animal was returned to atmospheric air, the QRS complex tended to return toward normal configuration and duration (Fig. 3, *E* and *F*). Leads I and II showed almost complete recovery, but, although the splinter almost entirely disappeared, the R deflection did not return to normal voltage in Lead III. The S-T segment, in the meantime, was inclined upward, and became incorporated in the greatly accentuated T wave which persisted until death. This was accompanied by a higher P wave, until, in Lead III, the three positive deflections were all of equal voltage.

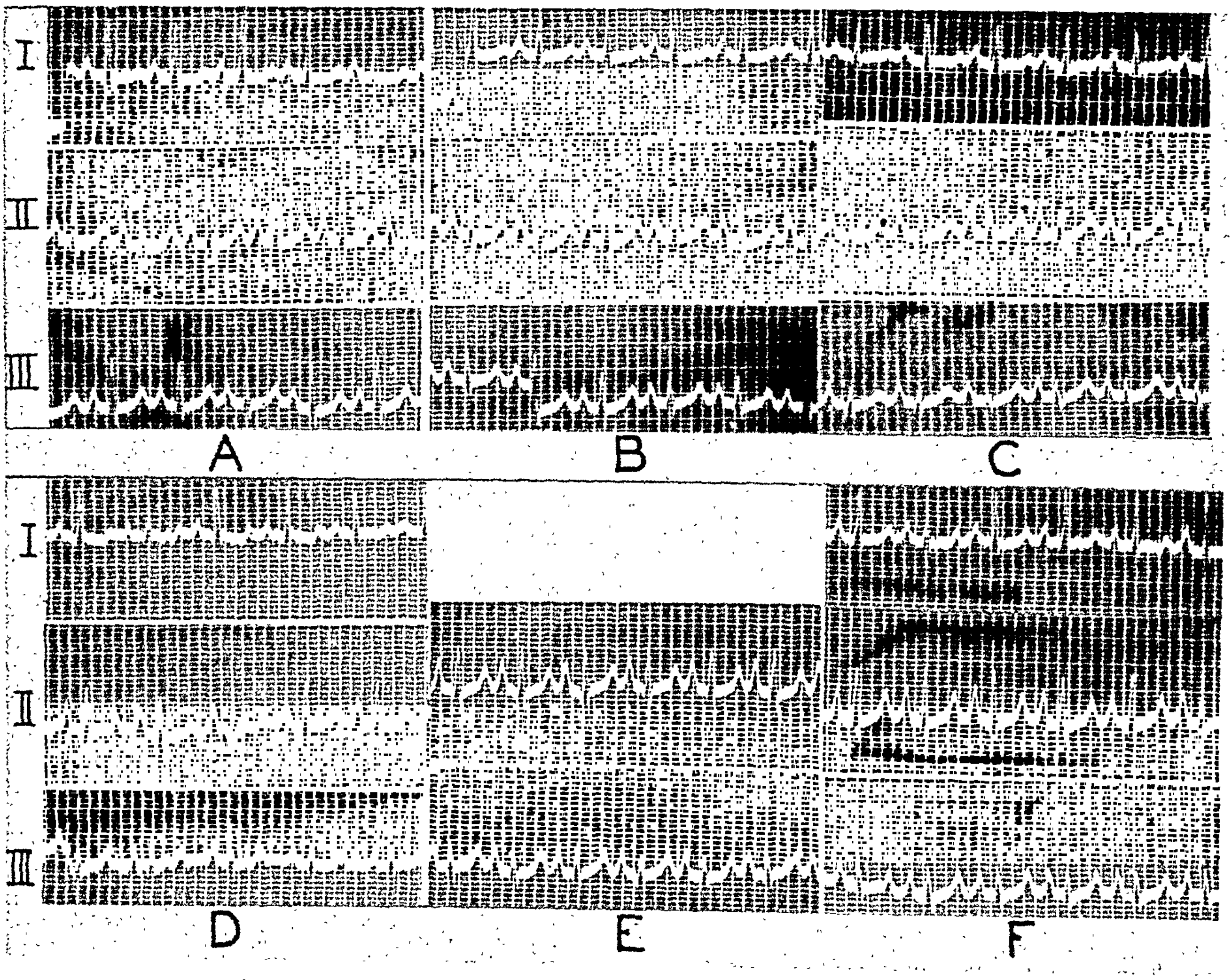

Fig. 3.—Segments of electrocardiographic records selected (as indicated in Fig. 2) from a continuous series taken throughout the experiment.

Fig. 4 illustrates the reactions of a "nontolerant" animal to sustained anoxia. It will be noted that the total respiratory and circulatory picture illustrates a lesser degree of resistance. In this experiment the oxygen percentage was decreased to only 12 per cent in forty minutes (simulating an ascent to 14,500 feet at a rate of 360 feet per minute). It was maintained thus for nearly three hours, when the percentage of oxygen was further decreased to 10 (altitude of 19,000 feet). Thirty minutes later collapse set in, and the animal was saved only by a prompt return to atmospheric air.

During the period of ascent and for an hour thereafter, respiration showed only a relatively mild stimulation, both in rate and amplitude, resulting in a twofold increase in minute volume. There was no progressive decline in minute volume at the end, as commonly noted, but rather a precipitous fall at the crisis. The type of failure, however, was much the same, i.e., hyperpnea was suddenly replaced by slow irregular breathing and apnea. The respiration was not continuously recorded in this experiment after the animal was returned to atmospheric air, but sufficient data from subsequent experiments indicated a return essentially to normal levels.

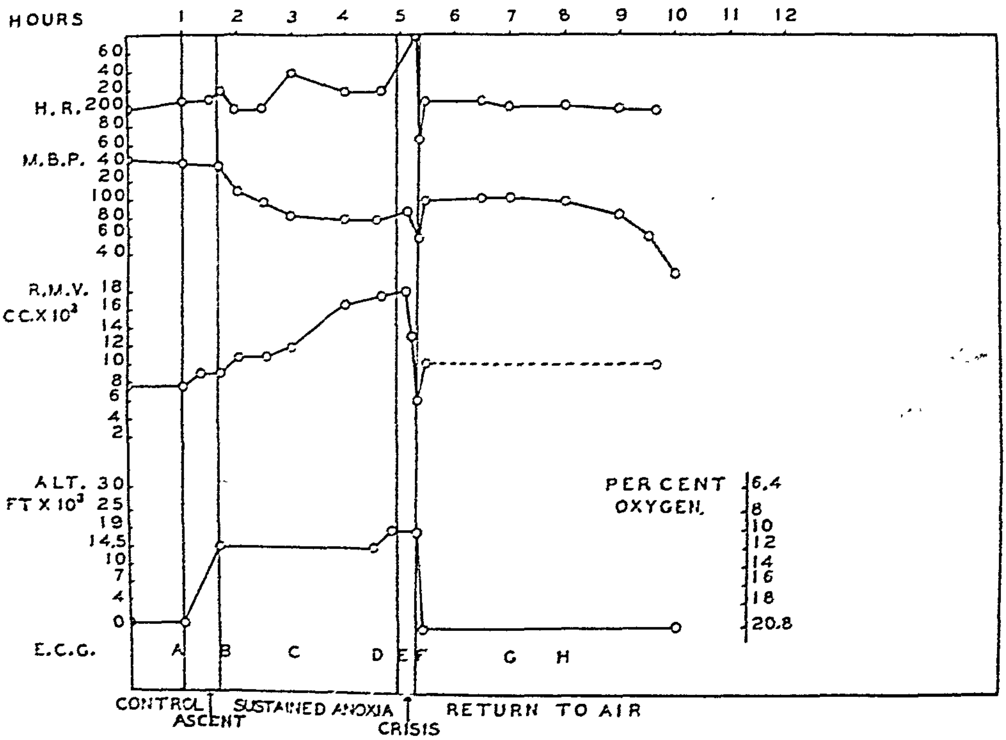

Fig. 4.—Responses of a normal, nontolerant dog to sustained anoxia. Legend remains as in Fig. 2.

The mean blood pressure failed to show an initial rise during the ascent, and did not rise above the starting level at any time. Rather, there was a progressive fall from the control pressure of about 140 mm. to 80 mm. Hg one hour and twenty minutes after reaching an altitude of 14,500 feet. This pressure was then maintained until complete failure at the crisis. Upon returning the animal to atmospheric air, the blood pressure rose to 100 mm. Hg, which was 40 mm. below the original starting control. Approximately this level was maintained for two hours and forty minutes, at which time a progressive fall began, which resulted in death of the animal two hours later. The heart rate showed inconsistent acceleration during the exposure at 12 per cent oxygen and marked acceleration at 10 per cent, followed by a sharp deceleration at the crisis. It resumed the control rate after the animal was revived and returned to atmospheric air.

Fig. 5.—Segments of electrocardiographic records selected (as indicated in Fig. 4) from a continuous series taken throughout the experiment.

Standard electrocardiograms were obtained, as indicated in Figs. 4 and 5 by the same letters. They show at a glance that the changes were much more striking during the period of sustained anoxia than those observed in the previously described experiment. Segments *B* and *C* show a progressive depression of the QRS complex in all leads, followed (segments *D* and *E*) by a polyphasic or M-shaped QRS complex in Leads II and III (Fig. 5). The apex of R_1 was slurred and depressed. Despite the severity of this polyphasic or splintering response, there was *no significant increase in the duration of the QRS complex, the* P-R interval, or electrical systole (Q-T interval) throughout the period of sustained anoxia.

The T waves of Leads II and III became progressively higher as the exposure continued. The increase was noticeable even during the ascent (Fig. 4, *B*), and the voltage finally reached was higher than that of the other complexes (Fig. 4, *D*). The P wave became merged with the descending limb of the T before the isoelectric level was reached. Just prior to collapse (Fig. 4, *F*), the T wave showed a changing configuration, varying from positive to negative. In many cycles the P was completely obliterated in both Leads II and III.

Returning the animal to air resulted in prompt improvement in all complexes until control levels were reached (Fig. 4, *G* and *H*). Despite this apparent return to normal, however, the animal died as a result of circulatory collapse. There were no definite subjective signs to give warning of imminent collapse during sustained anoxia. There was neither dyspnea nor convulsive muscular contractions, thus showing a sharp differentiation from asphyxial death, and animals were sometimes lost because of the sudden onset of respiratory and circulatory failure. After failure occurred, the animal could generally be revived by prompt artificial respiration.

DISCUSSION

It may be observed that tolerant animals show no significant depression of the heart and mean blood pressure until just before the crisis is reached. At this time changes are sudden and severe, as evidenced by a great reduction in heart rate and blood pressure, together with the conduction disturbances so well analyzed by Greene and Gilbert.[5-7] These variations are illustrated in Fig. 2, which represents exposure to an altitude of 27,000 feet for more than four and one-half hours. In nontolerant animals, however, a progressive decline in arterial pressure, often extending over the entire period of exposure, eventually terminates in the same type of crisis. This type of reaction is illustrated in Fig. 4, which represents exposure to an altitude of 14,500 to 19,000 feet for three and one-half hours. That considerable individual variation exists among experimental animals is not surprising in view of the fact that similar variations have been repeatedly demonstrated in pilots in training.

The effects of anoxia, therefore, appear to be accumulative, as emphasized by Armstrong and Heim,[4] but the manner in which the dog succumbs after release from long exposures depends upon the innate resistance of the animal.

When the animal was restored to atmospheric air or when oxygen was administered, there was always some recovery of mean arterial pressure, followed by subsequent decline to shock levels and, eventually, death. In tolerant dogs, the recovery was generally more marked and the subsequent decline in pressure more delayed than in nontolerant animals.

The cause of the variable deterioration in mean pressure during sustained anoxia remains essentially unknown, but two possible explanations invite investigation: (a) failure of the peripheral circulatory system and (b) cardiac depression. This investigation does not attempt to explore the former possibility, but may furnish some information concerning the latter. The development of depressed and splintered QRS complexes in electrocardiograms might lead one to suspect some mild but progressive myocardial disturbance, the nature of which cannot be interpreted too precisely. Detailed study of the electrocardiogram, however, fails to reveal any signs of delayed or impaired conduction. There is evidence, on the contrary, that conduction is slightly improved, at least in the earlier stages of the exposure. This evidence is, of course, the shortened P-R interval and the decreased duration of the QRS, in spite of the splintering. This certainly does not suggest damage to the conduction system; on the contrary, it could be regarded as improvement. If, as many believe, a shortened QRS indicates a more rapid spread of excitation over the ventricles, it could be postulated that a more rapid summation of fractionate contractions takes place, and that this eventuates in a more vigorous contraction of the ventricles.[22] This may then explain the preliminary stimulation of the heart reported by Sands and DeGraff,[19] and the increased stroke volume reported by Strughold.[20] The splintering, also, is not necessarily indicative of asynchronous spread of the excitation process, but could easily result from slight differences in summation of ultimate potential differences. Much more positive evidence, e.g., such as can be obtained by direct punctate leads from the heart with differential electrodes, is required before much clinical significance should be given to splintering of the QRS complex.

Contrary to most of the recent reports as to the electrocardiographic changes in men who are exposed to high altitudes, the S-T segment and T wave were not depressed. They are in accord, however, with the observations of Kountz and Gruber,[18] and revealed elevation of the S-T segment and increase in magnitude of the T wave. Since either change may be encountered subsequent to acute coronary occlusion, these observations are highly suggestive of anoxic impairment of the myo-

cardium. The fact that such changes occur more promptly and conspicuously in nontolerant animals during sustained anoxia suggests that the myocardium is an important factor in the problem of tolerance to high altitudes. However, the facts that the electrocardiographic deflections are gradually restored to normal upon return of the animal to atmospheric air, and that they remain so to the end, suggest that the progressive decline of blood pressure which follows subsequently is due to peripheral rather than cardiac factors.

SUMMARY

1. A simple form of rebreathing spirometer is described which is suitable for varying the rate of oxygen reduction (rate of simulated ascent) and for maintaining the ultimate percentage of oxygen breathed (theoretical attained altitude).

2. Dogs anesthetized with sodium barbital vary greatly in their resistance to sustained anoxia, and can definitely be placed in tolerant and nontolerant groups as regards the "altitude" and duration of exposure which they can endure.

3. Differences in responses in the two groups were not marked during the period of "ascent," except that the nontolerant group did not seem to increase their respiratory minute volume as early.

4. During sustained anoxia and until the sudden crisis, *tolerant dogs* showed acceleration of the heart, an essentially normal mean arterial pressure, a reduction in amplitude of the QRS deflection in all leads, and slight decreases in the duration of the P-R interval, QRS deflection, and electrical systole. On returning the animals to atmospheric air after the crisis, there was good but rarely complete recovery in blood pressure, but after six to twelve hours most of the dogs passed slowly into a state of circulatory failure. In this kind of circulatory failure there was no evidence in the electrocardiograms that failure of the myocardium was concerned.

5. *Nontolerant dogs,* even when maintained at lesser degrees of anoxia or for shorter periods, generally showed less increase in minute respiratory volume and a gradual decline of mean pressure during the sustained low-oxygen period. In addition to the changes shown by tolerant animals, the electrocardiogram often showed marked splintering of QRS in several leads (usually Leads II and III), elevation of the S-T segment, and/or increase in the T wave, which often equaled that of R. These changes were reduced and often abolished on returning the animals to atmospheric air.

6. Although the circulatory failure which followed exposure of dogs to sustained anoxia was apparently due to peripheral circulatory factors, the changes in the electrocardiogram were sufficiently conspicuous to suggest strongly that the response of the myocardium during exposure is an important factor in determining tolerance to sustained anoxia.

Acknowledgment is gratefully given to Dr. Carl J. Wiggers for suggesting this problem and for his kindly advice and assistance in preparing the manuscript.

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SARCOIDOSIS OF THE HEART

Report of a Case and Review of the Literature

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THE early observations on the disease which is now termed sarcoidosis suggested that it was solely a disease of the skin.[1, 2] However, since Schaumann[3] indicated, in 1914, that the disease may involve the internal organs of the body, the generalized nature of the disease has been recognized, and now it is known that practically any organ in the body may be involved. The case to be reported was one of generalized sarcoidosis which was unusual in that extensive involvement of the heart produced the most serious symptoms and caused the death of the patient. We have reviewed the literature with particular reference to demonstrated cardiac lesions and the symptoms which were directly related to these lesions.

CASE REPORT

L. D., Negro, male, aged 24 years; Unit Number 020-121.

This patient was admitted to Freedmen's Hospital Nov. 24, 1941, complaining: "I have trouble getting my breath." The study of his case revealed the following pertinent facts:

Family History.—Father dead of unknown cause; mother and one sister living and well; one sister chronically ill, and one dead of chronic disease, causes unknown; wife and three children living and well, and had negative chest roentgenograms.

Past History.—Excellent health until onset of last illness.

Last Illness.—Initial symptoms of headache and cough began in April, 1941, about eight months prior to death. When he was examined at another hospital because of these complaints, his temperature was normal and physical examination was negative, although roentgenograms of the chest showed enlarged mediastinal nodes. In May, 1941, additional symptoms appeared, namely, blurring of vision, loss of taste on the left side of the tongue, numbness and weakness of the left side of the face, difficulty in speaking, and defective hearing on the left. Physical examination at the same hospital showed involvement of the seventh, eighth, and twelfth nerves, and disclosed papilledema of the left disc, coarse tremors of the hands, fine râles at the base of the right lung, and a normal temperature and pulse rate. Roentgenograms showed increased size of the mediastinal nodes, together with pulmonary infiltration, particularly of the right lower lobe (Fig. 1). Tuberculin tests and repeated sputum examinations for tubercle bacilli were negative. The patient was discharged from the hospital after one month, at which time he showed but little improvement. Examination at another hospital in October, 1941, because of

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Received for publication April 3, 1943.

progressive loss of vision, showed large vitreous floaters, pigment deposits in the lenses, and vision as follows: O.D., 20/50, and O.S., 20/70. A tentative diagnosis of Boeck's sarcoid or tuberculous uveitis was made. Intermittent attacks of palpitation and tachycardia, associated with fainting spells, began to occur in August. 1941. Dyspnea on exertion, and then orthopnea, began in November, 1941, by which time patient had noted considerable weight loss.

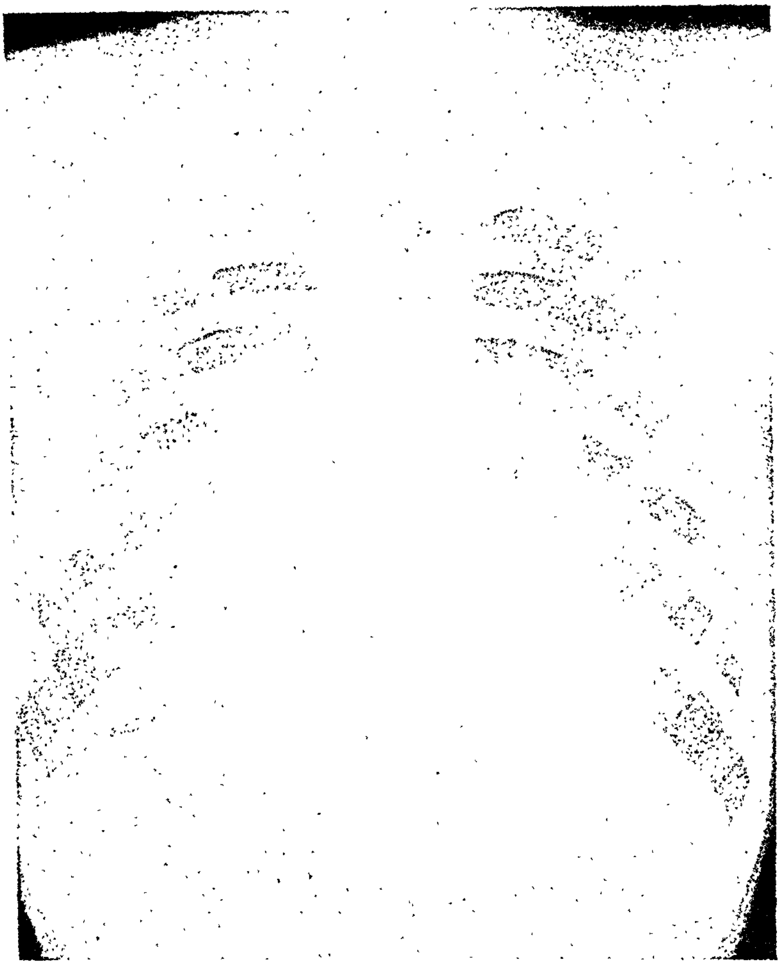

Fig. 1.—Dense lesions involving mediastinal nodes, merging with, and partly obscuring, the cardiac borders, and spreading out into the lungs.

Physical Examination.—The patient appeared chronically ill. He had orthopnea, moderately distended jugular veins, an enlarged and tender liver, medium râles, but no consolidation, at the bases of the lungs, slight edema of the lower extremities, a rectal temperature of 37.6° C., a pulse rate of 90, and a blood pressure of 100/65. The heart was enlarged to the left anterior axillary line, and there was bilateral widening of the supracardiac area of dullness; the heart showed an irregular irregularity, with rapid changes in rate, and, at times, a rapid and regular tachycardia, but, more usually, a slower rate, with many premature beats; there was a pulse deficit of 75. The venous pressure was 240 mm. of water, the circulation time, 55 seconds, and the vital capacity, 28 per cent of normal.

Laboratory Data.—The blood Wassermann reaction was negative. The hemoglobin was 80 per cent (Sahli); the erythrocytes numbered 5,470,000, and the leucocytes, 10,500. The differential leucocyte count was normal. The total plasma protein was 7.1 per cent. The urine was normal. The roentgenograms showed enlargement of the heart

and increased density at the bases of both lungs. There was no increase in the size of the mediastinal nodes (Fig. 2). The electrocardiograms showed evidence of marked ventricular irritability, with premature ventricular beats from multiple foci, and paroxysmal ventricular tachycardia. The sound tracing was difficult to interpret (Figs. 3 and 4).

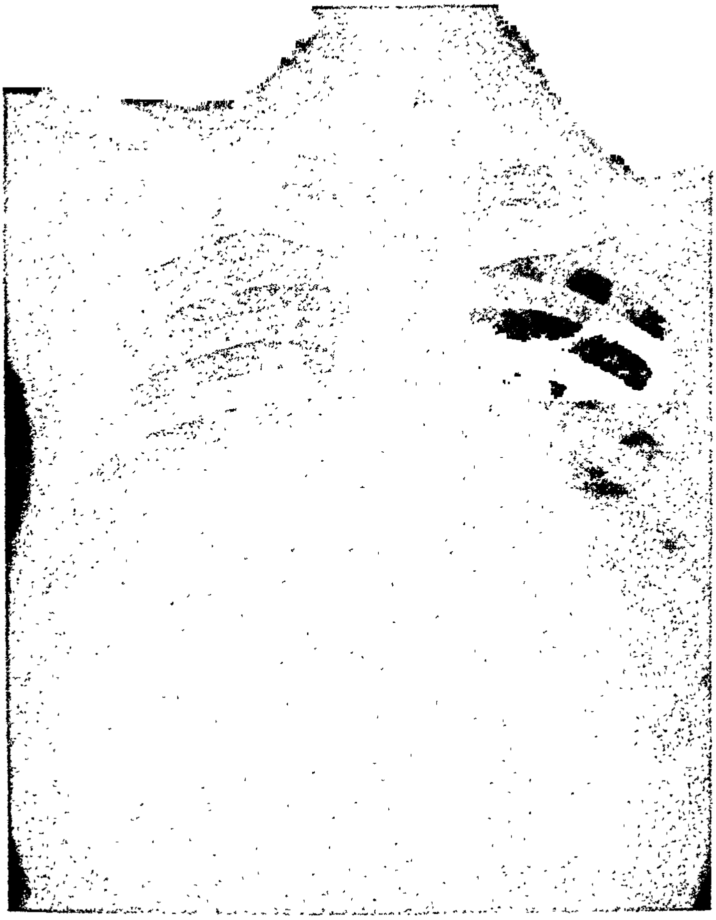

Fig. 2.—Dense lesions involving mediastinal nodes, marked enlargement of heart, increased density of bases of lungs.

Hospital Course.—In addition to sedatives, the patient was given 3 Gm. of quinidine sulfate in 72 hours. There was no improvement in the cardiac mechanism. On the fourth hospital day the patient developed a temperature of 38.5° C. and a severe cough, with blood-tinged sputum in which a Type 28 pneumococcus was found. There were more râles, especially in the right, lower, lateral part of the chest. He was thought to have pulmonary infarction or bronchopneumonia. Sulfadiazine was given, and its blood level was 4 mg. per cent at the end of 48 hours, but the temperature continued to be about 39° C. for four days. The signs of congestive failure increased. Oxygen was given. The cardiac irregularity continued, with a pulse deficit of 75. The quinidine was increased to 1.2 Gm. daily, after which the electrocardiogram showed longer periods during which the mechanism was normal. Pulmonary edema became severe on the ninth hospital day; phlebotomy (300 c.c.) was done, and six cat units of digalen were injected intramuscularly. During the next three days there was much

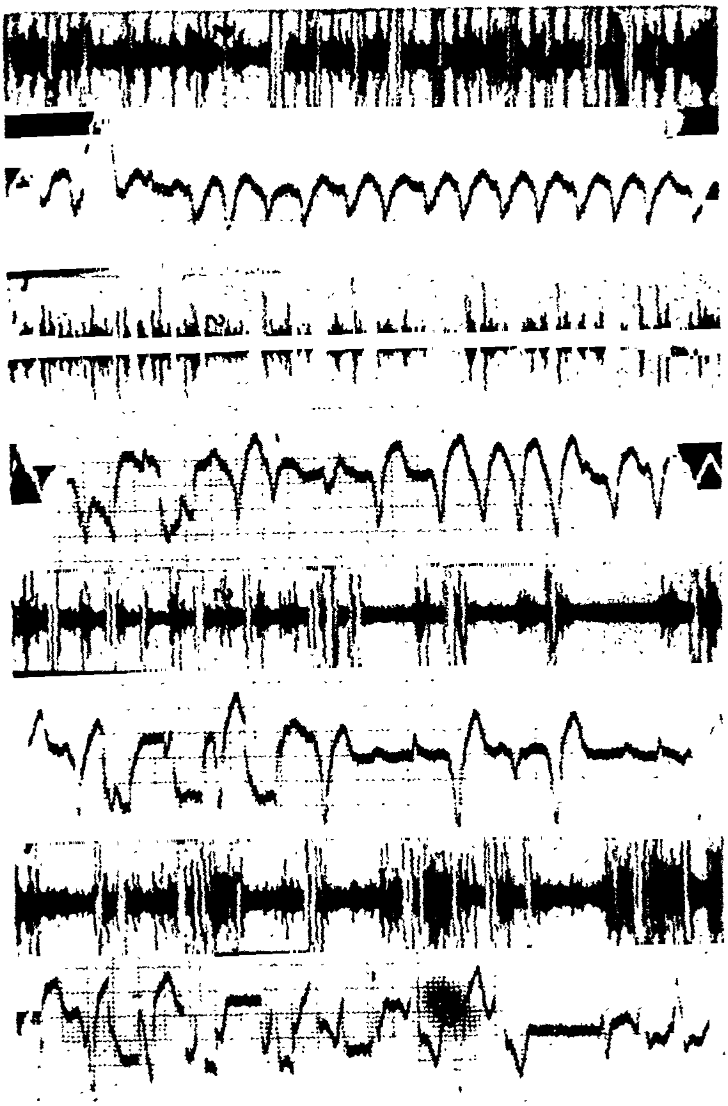

Fig. 3.—Electrocardiogram showing transient ventricular tachycardia and periods of premature ventricular beats from multiple foci. Several prolonged P-R intervals are present (0.28 second).

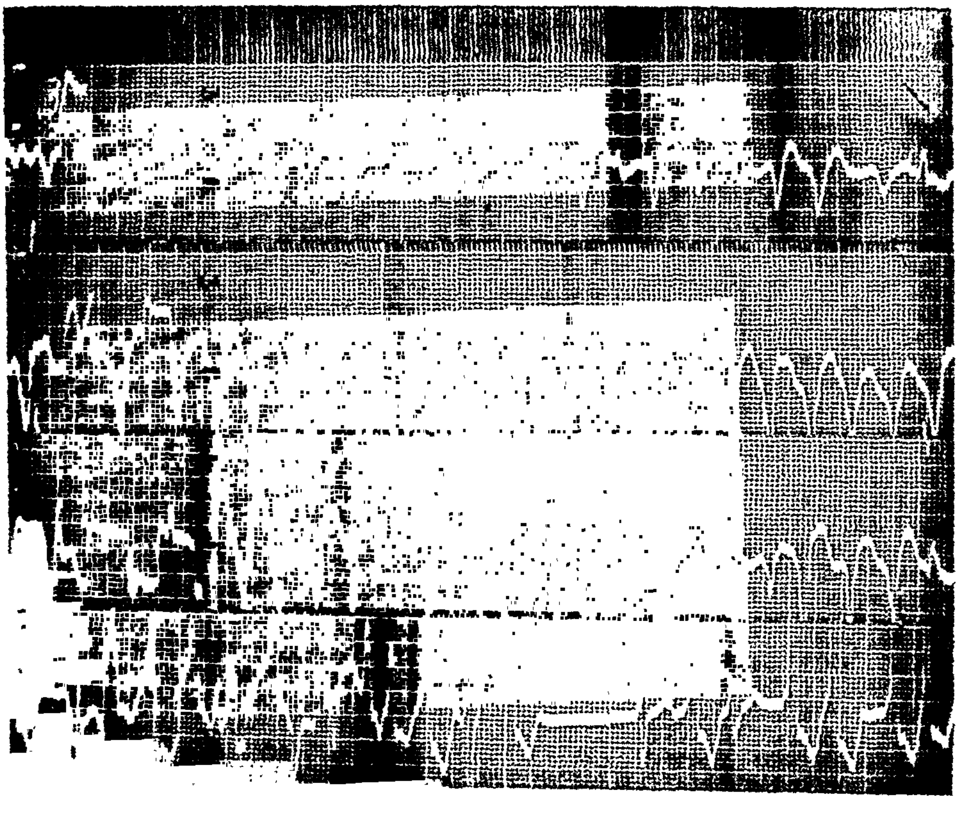

Fig. 4.—Electrocardiogram showing premature ventricular beats from multiple foci, and transient ventricular tachycardia.

improvement. However, on the twelfth hospital day the patient had a chill and became disoriented. He died suddenly on the thirteenth hospital day.

Clinical Impressions.—(1) Mediastinal tumor (type unknown), with probable extension into the myocardium; (2) ventricular irritability, with premature ventricular beats and paroxysmal ventricular tachycardia; (3) congestive heart failure; (4) pulmonary infarction or bronchopneumonia.

AUTOPSY

The autopsy was begun fourteen hours after death, and revealed the following significant gross changes:

Externally.—Dryness and some desquamation, but no nodular lesions of the skin; edematous swelling of the preauricular part of the left side of the face; slight enlargement of the left breast; petechiae over the left clavicle; cyanosis of the nail beds and distention of the jugular veins.

Abdominal Cavity.—About 150 c.c. of slightly bloodtinged fluid, with strands of fibrin, but no nodular lesions.

Pleural Cavities.—About 500 c.c. of similar fluid in the right pleural cavity and 110 c.c. in the left; granular lesions, resembling miliary tubercles, involving the visceral pleura, and fibrous adhesions involving the posterior and lateral pulmonic surfaces.

Pericardial Cavity.—About 100 c.c. of similar fluid.

Circulatory System.—The large arteries and veins of the trunk were apparently normal. Heart (Fig. 5): weight, 500 grams; thickness of the left ventricle, 10 to 20 mm., and of the right, 5 to 7 mm.; hyperemic epicardium, with multiple small and coalescing, granular, tubercle-like lesions; large epicardial scar at the apex anteriorly, with raised central plaque and a hemorrhagic border; myocardium soft and mottled in color because of hyperemia; small, grayish, tubercle-like lesions, and pink, myxomatous-like scars, 5 to 7 mm. in diameter; no valvular sclerosis. Valve orifices: tricuspid. 12 cm., pulmonic, 6 cm., mitral, 9 cm., and aortic, 5.5 cm., in circumference; mural apical thrombus of the left ventricle.

Respiratory System.—Frothy, mucoid, and slightly purulent exudate in the tracheobronchial passages. Lungs (Fig. 6): weight together with bronchi, lower trachea, and mediastinal lymph nodes, 1,800 grams; many small and coalescing, tubercle-like lesions, slightly raised above the pleural surface, and measuring 2 to 4 mm. in diameter; focal, reddish areas suggestive of infarction; recent scars involving the pleura and extending into the lung tissue from 1 to 3.5 cm.; cut surfaces showed edema, many tubercle-like lesions, small scars, and slight lobular consolidation.

Spleen and Lymph Nodes.—Spleen slightly enlarged and moderately soft, with scattered, small, tubercle-like lesions, but these were not palpable as nodules. Tracheobronchial lymph nodes (Fig. 6) enlarged and seemed to coalesce, forming a mass 8 cm. in maximum diameter and extending around the right main bronchus. Moderate enlargement of the lymph nodes around the head of the pancreas; other lymph nodes not enlarged.

Digestive System.—Passages normal except for petechiae of the stomach and duodenum; liver weighed 1,850 grams, had accentuated lobular

Fig. 5.—Shows widespread myocardial lesions and an apical mural thrombus.

Fig. 6.—Lungs, lower trachea, main bronchi, and tracheobronchial lymph nodes. Many small tubercle-like lesions appear on the lung surfaces, associated with localized scars and remnants of fibrous pleural adhesions. The lymph nodes are enlarged, forming a large mass.

markings caused by passive congestion; gall bladder, bile ducts, and pancreas normal.

Urinary System.—Kidneys weighed, together, 350 grams; there was a small infarct in each one, and slightly adherent capsules; ureters normal; ecchymoses of the bladder mucosa.

Brain and Meninges.—No gross abnormality.

Generative Organs.—Normal.

Endocrine Glands.—(Hypophysis, thyroid, and adrenal.) Normal.

On *microscopic examination,* tubercle-like lesions were found in the heart, lungs, lymph nodes, spleen, liver, and testes, whereas the pancreas, hypophysis, thyroid, adrenals, kidneys, breast, bone marrow (from one rib), and the brain did not reveal these lesions. The myocardium and, to a far less extent, the endocardium and epicardium were observed to be the seat of a chronic granulomatous inflammation. The earliest and smallest lesions consisted of an infiltration of lymphocytes and a few microphages into the stroma between and about muscle fibers (Fig. 7). In older lesions the muscle fibers had disappeared, and their site was occupied by large mononuclear epithelioid leucocytes and giant cells, with a peripheral border of lymphocytes, but without microphages (Fig. 7). At this stage the lesions bore a superficial resemblance to miliary tubercles, without caseation. When the lesions coalesced, many small capillaries were seen. The oldest lesions showed gradual replacement of the epithelioid and other cells by fibroblasts, leading eventually to scarring. Some of the scars were old; others were relatively young, and, at their margins, progression of the inflammation was apparent (Fig. 8). Occasionally, small blood vessels were occluded by thrombi; some showed inflammation of their walls, and one or two contained giant cells in their lumina. In one section, taken from the apex of the ventricle, there was a mural thrombus undergoing organization. In a section from near the base of the interventricular septum, the inflammatory process did not involve the more superficial muscle fibers.

All sections of the lungs showed small lesions which were indistinguishable morphologically from noncaseating miliary tubercles (Fig. 9). These involved the fibrous framework, alveolar walls, and alveolar lumina of both lungs, and they varied from early lesions to old ones undergoing hyalin sclerosis. The less involved portions of the lungs showed edema, focal deposits of fibrin, and extensive, but not heavy, infiltration of alveoli by macrophages. In three sections there were subpleural lesions of large size, undergoing hyalinization and infarct-like necrosis, with a preservation of the tissue pattern in the involved parts. The areas which, grossly, simulated infarction showed only hemorrhage microscopically.

The enlarged lymph nodes were involved almost entirely by an inflammatory process like that in the heart and lungs; it spared the capsules and did not appear to extend into adjacent tissues. Giant cells were found in abundance, but there was no caseation in the tubercle-like lesions.

In the liver, in addition to typical, tubercle-like lesions, there were others consisting of a few microphages, lymphocytes, and some macrophages. The testes revealed, in addition, acute inflammation of the arterial walls, with the cellular reaction of the more acute lesions.

Cultures made from the spleen and lungs were reported to have yielded growths of *Streptococcus hemolyticus, Staphylococcus aureus* and pneumococci (not typed), but no acid-fast organisms. Acid-

Fig. 7.—Heart: the earliest lesions consist of infiltrations of leucocytes in the stroma between muscle fibers; older ones consist of epithelioid cells and giant cells in a stroma which replaces destroyed muscle fibers.

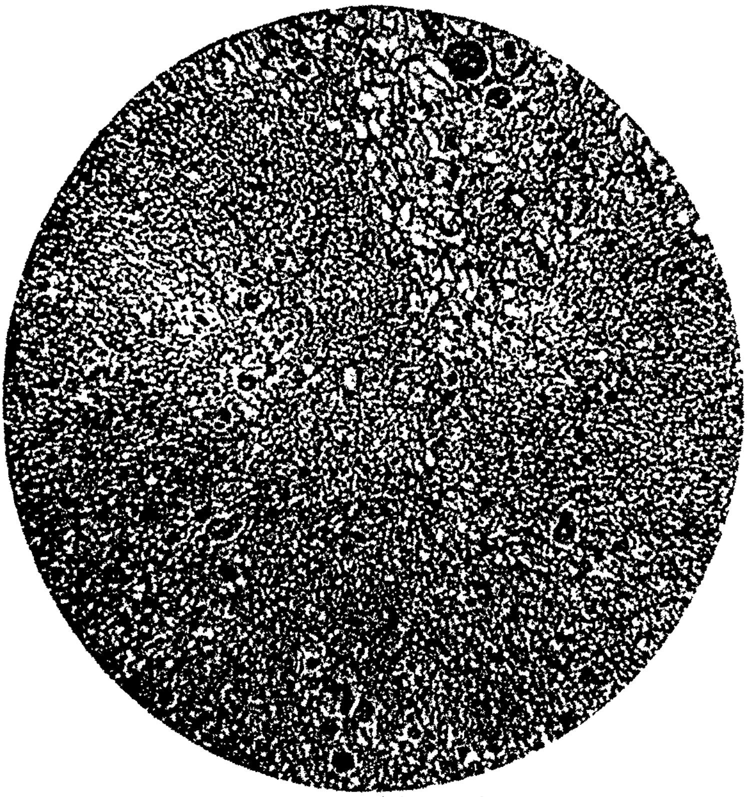

Fig. 8.—Heart: a well-vascularized scar is shown, at the margin of which is the spreading inflammation with tubercle-like lesions. A giant cell appears near the center of the figure.

fast and Gram stains on the sections of the heart and lymph nodes, as well as the lungs, failed to reveal bacteria or other parasites in the tubercle-like lesions.

Anatomic Diagnoses.—Active, healing, and healed, noncaseating tubercle-like lesions affecting the myocardium, epicardium, and endocardium, visceral pleura, lungs, spleen, liver, thoracic and upper abdominal lymph nodes, and testes—Boeck's sarcoid; dilatation, hypertrophy, and left ventricular mural thrombosis of the heart; bilateral renal embolism and infarction; bilateral pulmonary infarction; organizing, slightly hemorrhagic, fibrinoserous pericarditis, bilateral pleuritis and peritonitis; degeneration of parenchymatous organs, with splenic softening; chronic passive congestion of viscera; edematous swelling of the right side of the face, and bilateral pulmonary edema; mucopurulent tracheobronchitis; terminal septicemia (hemolytic streptococci and pneumococci); petechiae or ecchymoses of the mucosa of the stomach, duodenum, and urinary bladder, and of the skin over the right clavicle; left gynecomastia.

Fig. 9.—Lung, showing a small tubercle-like lesion adjacent to a large vein.

This patient presented the typical lesions of sarcoidosis, although the unusually rapid course and the severity of symptoms were quite in contrast to the usual picture in sarcoidosis. The extensive cardiac involvement was undoubtedly responsible for these two atypical features of the disease in this patient.

REVIEW OF THE LITERATURE

A study of the case reports of generalized sarcoidosis reveals very few cases in which cardiac lesions have been demonstrated at autopsy. Bernstein, et al.,[4] reported a case in which lesions were found in the

epicardium and myocardium. There was no clinical evidence that these lesions produced any abnormality of cardiac function. In the second of the four autopsy cases presented by Schaumann,[5] in 1936, there were many lesions of the heart which were limited, apparently, to the epicardium. The lungs were extensively involved by a chronic granulomatous inflammation, and showed many sclerosed and obstructed vessels and considerable emphysema. The patient had a long history of palpitation, and, during the last year of life, congestive heart failure developed; the blood pressure was 110/88; the electrocardiogram showed right ventricular preponderance and inversion of T_2 and T_3. Schaumann expressed the opinion that the cardiac failure was secondary to the increased pulmonary resistance caused by the extensive lesions in the lung parenchyma. In the first of the six autopsy cases reported by Nickerson,[6] in 1937, there were typical lesions of the parietal pericardium. Solitary lesions were found also in the myocardium and subendocardium. There had been no cardiac arrhythmia. There was dyspnea, but the patient had pleural effusion as a result of sarcoid involvement of the pleura. The electrocardiogram was not reported. Spencer and Warren[7] reported a case of generalized sarcoidosis in which microscopic lesions were found scattered throughout the myocardium. There was no clinical evidence of cardiac involvement. No electrocardiogram was reported. Cotter[8] reported a case which was similar in many respects to the case presented here. The course was rapid, and the patient died of cardiac failure caused by extensive sarcoidosis of the heart. The heart was enlarged and there was precordial bulging. The blood pressure was 140/110. Congestive heart failure was marked. The electrocardiogram showed a variety of abnormalities during the hospital course: sinus tachycardia, arborization block, shifting pacemaker, auricular fibrillation, and complete heart block. At autopsy the epicardium and pericardium were normal, but the myocardium was extensively infiltrated by typical sarcoid lesions. The endocardium was also involved, including sessile nodules on the mitral valve.

In three of the four autopsy cases reported by Longcope,[9] in 1941, there were lesions of the myocardium. In one of the cases, scattered nodules were found in the myocardium, but clinically the patient showed neither signs nor symptoms of cardiac disease. A second patient who had had no known previous cardiac symptoms dropped dead on his doorstep. Autopsy showed extensive infiltration of the pericardium with sarcoid tissue, but the other structures of the heart were not involved. The third patient had sarcoid nodules scattered throughout the pericardium and myocardium. In addition, there was a large scar in the interventricular septum which probably accounted for the ten-year history of Adams-Stokes syndrome and the complete auriculoventricular dissociation which was shown by the electrocardiogram. In view of the history of syphilis and of the fact that the pa-

tient had received antisyphilitic treatment, the author could not exclude syphilis as the cause of the scar. Premature beats were also seen in the electrocardiogram.

Many clinical reports, without autopsy, have indicated the presence of cardiac abnormalities in patients with sarcoidosis. In two of the four cases reported by Salvesen,[10] in 1935, there were changing abnormalities in cardiac mechanism. There were repeated attacks of paroxysmal tachycardia and severe palpitation in Case 3. The electrocardiogram showed inversion of T_2 and T_3. The heart was normal in size in Case 4, but the cardiac mechanism was abnormal. The electrocardiogram showed transient right bundle branch block, with premature beats in the form of bigeminy. Tachycardia was rather constant. The patient was treated with quinidine chloride for seven days, after which the bundle branch block disappeared. However, exercise and amyl nitrite caused return of the block. Harrell[11] reported electrocardiograms in eight cases in which there were no cardiac symptoms. No changes in mechanism were found. Longcope and Fisher[12] stated that three of their unautopsied patients had evidence of myocardial damage and cardiac enlargement. Other case reports list dyspnea on exertion as a symptom, but, in these instances, mediastinal masses or pleural effusion, or both, were present, and could well have accounted for this symptom. It seems likely that some of these patients may have had sarcoid lesions of the heart, especially those who had striking and variable changes in cardiac mechanism. However, in the absence of autopsy confirmation, the other, more common, causes of cardiac disease cannot be excluded. This is well illustrated in Schaumann's[5] third case, in which the patient had tachycardia, premature beats, and low voltage in Leads I and III, but at autopsy no evidence of sarcoid lesions was found in the heart.

A review of the case reports of Boeck's sarcoid with cardiac lesions is hampered by the lack of uniformity in diagnostic criteria and the fact that many authors are of the opinion that sarcoidosis is a proliferative and noncaseating type of tuberculosis. The evidence for this concept of sarcoidosis is discussed in detail by Pinner.[13] Garland and Thomson[14] reported a case of uveoparotid tuberculosis in which there was massive involvement of the visceral pericardium and myocardium. This case meets all of the criteria for sarcoidosis. Both eyes and parotids were involved; the von Pirquet test was negative; at autopsy, disseminated lesions were found in the parotids, liver, kidneys, lungs, uterus, and heart. The microscopic picture was typical. No evidence of caseation was found in any of the lesions. Repeated Ziehl-Neelsen stains of the lesions were negative for acid-fast organisms. The patient had had dyspnea, but no arrhythmia. No electrocardiogram was reported. Another case of uveoparotid fever was reported by Thomson[15] in 1930; it meets all of the criteria for a diagnosis of sarcoidosis

of the heart except for the fact that acid-fast bacilli were found in one of the slides from macerated pieces of the myocardium.

In the case reported by Taussig and Oppenheimer[16] as one of severe myocarditis of unknown cause, there were disseminated, tubercle-like lesions in which no tubercle bacilli could be demonstrated. However, this patient did have a positive tuberculin test and there was necrosis in some of the lesions. Jonas[17] described five cases of granulomatous myocarditis, including that reported by Taussig and Oppenheimer. Case 3 of this group, in which the patient had a rapid course, a negative tuberculin test, recurrent attacks of paroxysmal tachycardia, and died suddenly, cannot be distinguished from some of the typical cases of sarcoidosis with cardiac involvement. Anatomically, the lesions were widely disseminated and tubercle-like, without caseation. Ziehl-Neelson stains of the lesions showed no acid-fast organisms. Guinea pig inoculations were negative. The other four cases are less suggestive of sarcoidosis in that, in Cases 2 and 5, there was considerable caseation, and the lesions in Cases 1, 4, and 5 were not regarded as typical tubercle-like lesions.

Hirayama[18] reported a case of specific myocarditis in which lesions were found in the heart, lungs, liver, and tracheobronchial nodes. Microscopically, the lesions were like noncaseous tubercles, and hence were typical of sarcoidosis. Studies for tubercle bacilli and spirochetes were negative. The patient had had recurrent attacks of shortness of breath and cardiac arrhythmia. In Brosig's[19] case the lesions cannot be distinguished microscopically from sarcoidosis. This patient died suddenly. No history was available. The mediastinal nodes and the heart, including the septum, showed extensive involvement. Studies for tubercle bacilli were negative. Brosig refers to several other cases in the earlier German literature which were of the same character as his, but were not reported as sarcoidosis. Undoubtedly there are other, similar cases in the literature which are typical of sarcoidosis, although they are reported as atypical tuberculosis, specific myocarditis, granulomatous myocarditis, or myocarditis of unknown cause.

SUMMARY

1. A case of generalized sarcoidosis in which there was massive infiltration of the myocardium is reported. The patient had had premature ventricular beats from multiple foci, paroxysmal ventricular tachycardia, and severe congestive heart failure.

2. Eight cases of sarcoidosis of the heart were found in a review of the literature. Clinical evidence of heart disease was present in three of these cases, and sudden death occurred in another. The electrocardiogram showed no characteristic changes, but in several of the cases of massive cardiac involvement there were pronounced abnormalities of the cardiac mechanism.

3. There seems to be little or no occasion to doubt that some of the cases reported as atypical tuberculosis, specific myocarditis, granulomatous myocarditis, and myocarditis of unknown cause were, in fact, cases of sarcoidosis of the heart.

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Clinical Reports

COR TRIVENTRICULARE*

Report of Case

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THIS case is being reported because the author has not been able to find a report of a similar congenital anomaly.[1] The specimen was shown to members of the Anatomy and Pathology Departments of the University of California and of Stanford University, who, likewise, could not recall seeing such a case.[6, 7]

CASE REPORT

History.—C. A. R., a white man, 23 years of age, was admitted to the U. S. Naval Hospital, Mare Island, May 17, 1942. For two months prior to his admission he had been under the care of the Naval Dispensary staff at Long Beach, where a diagnosis of congenital heart disease, with subacute bacterial endocarditis, was made, and, on two occasions, *Streptococcus viridans* was recovered from the blood.

On admission to the hospital, the patient gave the following history: In December, 1941, he developed severe, daily headaches and felt feverish every day. In January, 1942, he developed right-sided pleurisy, and, two weeks later, had pleuritic pains in the left side of the chest. He was hospitalized and continued to have daily afternoon fever, with attacks of pain in his abdomen and chest. He had occasional attacks of precordial pain, dyspnea, and palpitation, and these grew worse. His past history revealed that he had had measles, mumps, rheumatic fever, and pneumonia. His mother further stated, "He has always had a bad heart."

Physical Examination (On admission).—The patient was a well-developed and well-nourished white man who appeared pale and tired. There was an area of dullness in the base of the left lung. The heart was not enlarged to percussion. The point of maximum impulse was in the fifth intercostal space within the midclavicular line. A thrill was palpable over the entire precordium, but was best felt over the third intercostal space on the left. The rhythm was regular and the rate was 88. A loud, harsh, blowing systolic murmur was heard over Erb's point, was transmitted to the right shoulder, and could be heard over the entire anterior surface of the left side of the chest. The spleen was palpable and tender.

Course in Hospital.—During his stay in the hospital, he grew steadily worse. He showed, at intervals, symptoms and signs of embolism of various organs, especially the lungs and kidneys. He ran a spikelike temperature curve, developed pleural effusion bilaterally, showed grad-

Received for publication April 18, 1943.

*The opinions and assertions contained therein are the private ones of the writer and are not to be construed as official or reflecting the views of The Navy Department or the Naval Service at large.

ual enlargement of his liver and spleen, and, finally, three days before death, had extensive purpura. His therapy consisted of the following:

1. Heavy doses of sulfonamides, at times resulting in a blood level of over 20 mg. per cent.
2. Repeated, whole-blood transfusions.
3. Opiates for both the precordial pain and the pain resulting from emboli.
4. Oxygen.

Laboratory Studies.—An electrocardiogram nine days before death showed no striking abnormality. There were sinus tachycardia (rate 124), right axis deviation, a P-R interval of 0.17 second, a QRS interval of 0.10 second, and depressed S-T segments in Leads I and II. Fluoroscopic and roentgenographic examination of the chest, shortly before death, revealed generalized cardiac enlargement, with a prominent conus and definite enlargement of the right ventricle. Blood cultures (taken before the use of sulfonamides) showed nonhemolytic streptococci. After the sulfonamides were given, six blood cultures were negative (however, no p-amino-benzoic acid had been added to the culture media to neutralize the sulfonamides in the blood). His erythrocyte count was generally about 3,500,000 despite repeated transfusions, and, at one time, fell to 2,900,000. As the patient began to develop edema of the lower extremities, his total protein (serum) fell to 4.17 per cent and his albumin/globulin ratio was 1:1.

Summary of Necropsy.—Died: Nov. 25, 1942, 4:09 A.M. Necropsy: Nov. 25, 1942, 9:30 A.M.

The body was that of a white man who appeared to be about 30 years of age (actual age, 23 years); it was about 71 inches in length and showed evidence of loss of weight. The right pupil was somewhat irregular. There was icterus (2 plus) which was quite marked in the sclera. Numerous petechiae were scattered over the skin, and some purpuric areas were present over the tip of the nose, the right sclera, and the middle toe of the right foot. There was 3 plus edema of the right foot, 2 plus edema of the left foot, and 1 plus edema of both legs. Necropsy was restricted to examination of the chest and abdomen.

Lungs and Pleural Spaces.—The diaphragm reached the fourth intercostal space on the right and the fifth intercostal space on the left. The left pleural space was completely obliterated by adhesions except for an area over the left upper lobe. There were dense pleuropericardial adhesions anteriorly on the left. Dense adhesions obliterated the right pleural cavity posteriorly. Each lung weighed 900 grams. There was a well-organized thrombus in the left pulmonary artery which occluded the entire lumen. A smaller thrombus was found in the right pulmonary artery. Both lungs showed numerous infarcts of various ages. Most of the infarcts were grayish-red and of fairly recent occurrence. There were quite marked pulmonary edema and congestion.

Pericardial Sac.—Free of adhesions and anomalies. Contained about 75 c.c. of bloodtinged fluid.

Heart.—Weight, 460 grams. Valvular measurements as follows:

A.V.	7.4 cm.	T.V.	13.7 cm.
M.C.	10.7 cm.	P.V.	9.0 cm.

Right ventricular wall, from 0.5 cm. to 1.7 cm. in thickness. Left ventricular wall, 1.9 cm. in thickness.

There was an anomalous septum dividing the conus arteriosus from the body of the right ventricle. The pulmonary artery thus led into a conical chamber which had a perforation in the upper portion of the septum for communication with the right ventricle (Fig. 1). This opening measured 1.5 cm. in diameter and had a firm fibrous margin which was covered by vegetations. There were two smaller openings in the lower portion of the septum (Fig. 1). These measured about 3 mm. and also led into the right ventricle. No vegetations were visible grossly over these lower openings. The wall of this chamber measured about 3 mm. The pulmonic cusps were covered by large, friable, cauliflower-like vegetations which extended downward on the endocardium to the large opening in the septum, described above. The remaining chambers showed no anatomic defects. There were small vegetations on the mitral valve (Fig. 3, arrow); more prominent vegetations were seen on the tricuspid and some on the aortic valve. There were small subendocardial purpuric areas in the right auricle and small petechiae in the epicardium.

Fig. 1.—Showing abnormal extra chamber (ventricle). Note cauliflower-like vegetations on pulmonary artery. Arrows indicate openings in anomalous septum, communicating with right ventricle.

The right auricle was dilated and the wall hypertrophied. The heart thus showed no external evidence of abnormal development, but contained a persistent septum which created a separate chamber from which

the pulmonary artery led. Blood passed into this abnormal chamber through an opening in the upper portion of the anomalous septum, and this led into the right ventricle (Fig. 5). The margins of this opening were fibrous and covered by vegetations. There was no defect in the interventricular septum. (The anomalous openings are visible in Figs. 1 and 2, which show the pulmonary artery, the anomalous chamber, and the right ventricle. Fig. 3 shows the left ventricle and mitral valve.)

Liver.—The inferior border reached 13 cm. below the xiphoid process and 7.5 cm. below the right costal margin. Weight, 1,900 grams. On cut section, no gross infarcts were found.

Fig. 2.—Right ventricle. Tricuspid valve folded back to show opening (arrow) leading from right ventricle to abnormal chamber.

Spleen.—Weight, 600 grams. The cut surface showed old and recent infarcts. The old infarcts were yellowish, wedge-shaped, and showed beginning organization.

Kidneys.—The right weighed 200 grams, and the left, 230 grams. The renal capsules were somewhat adherent. On stripping the capsules, several moderate-sized, grayish-red infarcts were visible on the cortical surface. Also, numerous small petechiae were seen on the surface. The main renal arteries were opened and no thrombi found.

Gastrointestinal Tract.—The stomach contained several hundred cubic centimeters of bloodtinged fluid. Particles of food were suspended in the fluid. The mucosa showed a number of small, pinhead-sized hemorrhages. There was a moderate-sized purpuric area in a loop of small intestine. The peritoneal cavity contained about 200 c.c. of bloodtinged fluid.

Anatomic Diagnoses.—(1) Congenital (embryonal) defect in heart; (2) anomalous septum formation in right ventricle; (3) perforations of anomalous septum; (4) valvular endocarditis, vegetative; (5) mural endocarditis; (6) infarction of lung, spleen, intestines, and kidney; (7) purpura; (8) cardiac hypertrophy and dilatation; (9) cardiac hepatomegaly; (10) cardiac splenomegaly; and (11) adhesive pleuritis, old.

Microscopic examination confirmed the gross diagnoses.

Fig. 3.—Left ventricle. Interventricular septum normal. Small vegetation on mitral valve (arrow).

DISCUSSION

This case presents further evidence of the occurrence of bacterial inflammatory processes in cardiovascular defects.[2, 3] Abbott points out that bacterial endocarditis is more likely to occur in those congenital heart lesions where there is mechanical obstruction to the flow of blood. Such areas act as a locus minoris resistentiae for invasion by microorganisms which circulate through the blood stream from time to time. In our case, there was definite obstruction to the normal flow, for the blood had to pass through a narrow opening (1.5 cm. in diameter) to

reach the pulmonary artery. Abbott found an incidence of 17.6 per cent of bacterial endocarditis in cases of congenital heart lesions, and further found that this complication was more frequent among patients who live to maturity (the age of our patient was 23 years).

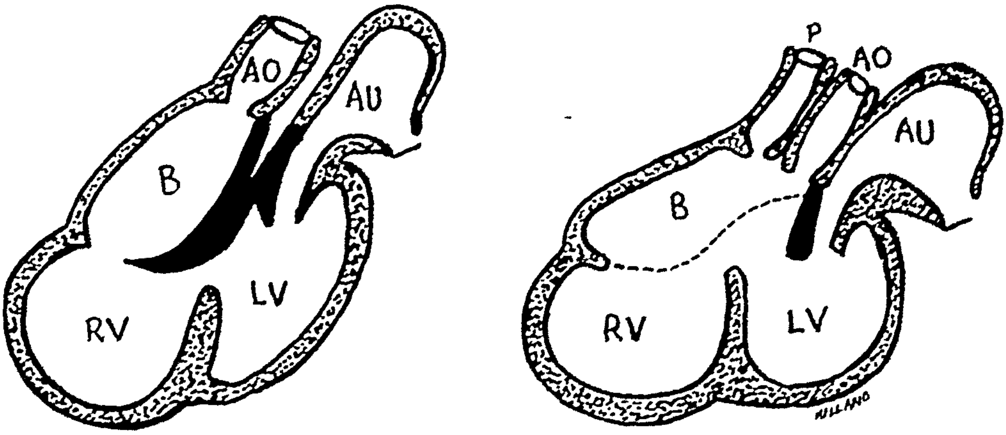

Fig. 4.—Illustrating transformation of bulbus cordis. *AO*, Primitive aortic stem; *B*, bulbus cordis; *P*, pulmonary artery; *AU*, auricle, left; *LV*, left ventricle; *RV*, right ventricle. (After Keith.)

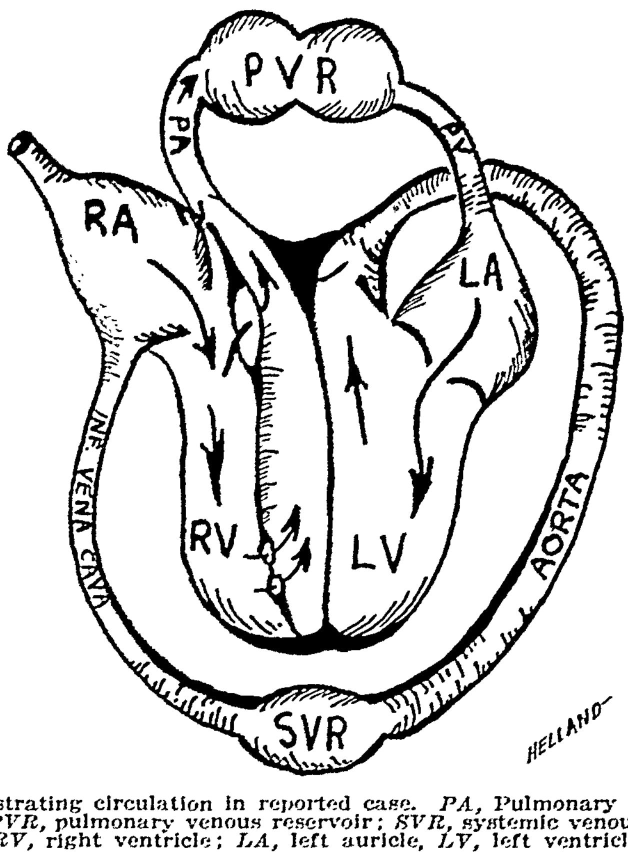

Fig. 5.—Illustrating circulation in reported case. *PA*, Pulmonary artery; *PV*, pulmonary vein; *PVR*, pulmonary venous reservoir; *SVR*, systemic venous reservoir; *RA*, right auricle; *RV*, right ventricle; *LA*, left auricle, *LV*, left ventricle.

Abbott and Dawson[4] published a clinical classification of congenital heart disease in which the cases were divided into three groups according to the mechanical effects upon the blood stream. Group 1 comprised cases without abnormal communication, but with strain, e.g., coarctation of the aorta. Group 2 included cases of arteriovenous shunt, e.g.,

patent ductus arteriosus, patent foramen ovale. Group 3 included cases of venous arterial shunt, e.g., cor triloculare biatriatum, persistent truncus arteriosus. Our case should probably be placed in Group 1, for the direction of blood flow was not actually changed, but there was strain at the narrow, abnormal opening in the anomalous septum.

As to the origin of the anomaly encountered in this heart, it would appear to be the result of persistence of the bulbus cordis. Sir Arthur Keith[5] has stressed the complicated changes that take place in the critical bulbar region, and Abbott adds, "The researches of Greil on the reptilian and Keith on the human heart, and of Jane Robertson on the fish show that the mammalian bulbus represents what was, at one time, an independent chamber with muscular walls and its own system of multiple valves which, in the 'ontogenetic telescoping of phylogenetic stages' has become submerged." This case may, therefore, be an example of a phylogenetic anomaly. Saunders,[6] in studying our case, stated, "There are two possible explanations: first, that there was some dichotomy of the original ventricular septum, the accessory portion dividing to the right and segregating the bulbus cordis; the other, that the septum of the truncus arteriosus instead of meeting the interventricular septum, has grown down to the right and separated off the accessory chamber." This latter possibility can be visualized by a study of Fig. 4. The direction of blood flow in our case is shown in Fig. 5.

SUMMARY

A case of an unusual congenital anomaly of the heart is presented. The apparent persistence of the bulbus cordis, which became segregated from the rest of the right ventricle, resulted in the formation of a third ventricle. No other developmental defect was found, and the interventricular septum was intact.

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CARDIAC INVOLVEMENT IN TRICHINOSIS: REPORT OF A CASE IN WHICH THERE WERE ELECTROCARDIOGRAPHIC CHANGES

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IN A COMPREHENSIVE review of the literature on the incidence of electrocardiographic changes as the result of myocardial damage caused by *Trichinella spiralis* infestation it was found that the reported percentage of abnormalities varied from 4.5 per cent[6] to 33 per cent.[1,2] Masters and Jaffe[16] state that 25 per cent of the patients have prolonged P-R intervals (0.22 second, maximum) and 33 per cent exhibit inversion of the T wave in Lead II. According to Spink,[1,2] the electrocardiographic evidence of myocardial damage in trichinosis is characterized by T-wave changes, which include initial flattening or inversion of the T wave, especially in Lead II, with later reversion to the upright position, low amplitude of the QRS complex, and intraventricular block. Electrocardiograms taken in a case described by Cushing[9] showed that the T waves were inverted in Lead II and upright in Lead IV. These changes gradually disappeared. Pardee[8] mentions that T-wave changes may occur in trichinosis. In their recent monograph, *Electrocardiography in Practice,* Graybiel and White[17] contend that there is rarely any alteration of the electrocardiogram, although in some cases there are long P-R intervals and abnormal T waves. Katz[18] makes no mention of electrocardiographic changes in trichinosis in his *Exercises in Electrocardiographic Interpretation.*

The purpose of this paper is to report a case of proved trichinosis, with associated electrocardiographic changes, including definite T-wave alteration in the standard leads and two precordial leads, namely, IVR and CR_5. To date, the patient has been followed for a ten-month period. Electrocardiograms were taken three times within a two-week period during the patient's hospital stay, and monthly thereafter, in the Cardiac Clinic of the Milwaukee County General Hospital.

REPORT OF CASE

History.—R. S., a 36-year-old white woman, entered the hospital complaining of generalized body aches, loss of strength, headaches, anorexia, nausea, vomiting, pain in the midepigastrium, chills, and fever, of two weeks' duration. On questioning, she admitted that she had eaten raw hamburger and tenderized ham recently on at least several occasions. The patient was apparently quite well until about two weeks before

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Received for publication April 19, 1943.

entry, when the above-named symptoms began and gradually grew worse. The initial symptoms consisted of pain in the midepigastrium which radiated bilaterally into the flanks and the back. This was accompanied by constant nausea, vomiting, and diarrhea. Shortly thereafter, the patient began to have pounding occipital headaches, and then developed generalized body aches, pains, and weakness, principally in the legs and arms, especially on movement. One week before entry, she noted marked swelling of the eyelids. Four days before admission the patient felt very weak and found that she was unable to walk. A fever of 101° F. appeared, together with chills, which necessitated her remaining in bed prior to going to the hospital. During this illness she had for the first time a precordial pain radiating into the left axilla. Her past history was unimportant except for a gall bladder operation four years previously.

Physical Examination.—Blood pressure, 126/74; pulse rate, 104; respiratory rate, 20; and temperature, 101.4° F.

The patient was well developed, well nourished, very lethargic, and exhibited flushed features. The body was warm and moist. The eyelids showed slight edema, but the conjunctivae were clear. The tongue appeared slightly swollen. The pharynx was injected, and showed hypertrophic lymphoid tissue. The chest was emphysematous and thick. The respiration was regular at 20 per minute. The lungs were clear and resonant. On percussion, the heart was not enlarged; the apical impulse was not seen or palpated; there were no thrills. Auscultation at the apex revealed tones of poor quality. There was a moderately rapid rate, 104 a minute, with sinus rhythm. No murmurs were heard. No abdominal organs were palpable. There was slight tenderness over the left calf.

Progress Notes.—During the first eleven days, the pain in the biceps, deltoids, and calves persisted, then became progressively less, and finally subsided completely. The patient was up and about after the fifth day, and during the whole period the heart sounds were of good quality. No arrhythmia was noted, and the patient had no cardiac complaints. On the second hospital day, and again on the twenty-third day, the skin test for trichinosis was definitely positive. Except for a temperature of 101.4° F. on the day of entry, and a temperature fluctuating between 99.6° and 98.6° F. for the succeeding three days, the patient remained afrebrile throughout her hospital stay.

The sedimentation rate by the Westergren method was 30 mm. for the first hour and 55 mm. at the end of two hours. The urine and stool examination revealed no pertinent abnormalities. The blood Wassermann and Kline reactions were negative.

On the second hospital day the hemoglobin was 15 grams, and the leucocyte count, 27,050, with 39 per cent eosinophiles. During the first three weeks of the disease, the leucocyte count fell gradually to 14,100, but the eosinophiles remained between 32 and 50 per cent. Three months later the eosinophile count had fallen to 3 per cent, and seven months later, it was 2 per cent.

Therapy consisted first of an obesity diet, and later of a high-calcium diet, magnesium sulfate, viosterol, and calcium gluconate. The patient recovered uneventfully and was transferred to the outpatient cardiac clinic of the Milwaukee County General Hospital.

Electrocardiographic and Roentgenographic Examinations.—Eleven days after entry into the hospital, or approximately twenty-five days

after the onset of the disease, the first electrocardiogram was taken (Fig. 1). It revealed sinus tachycardia, definite left axis deviation, a slightly depressed S-T segment in Lead I, an inverted T wave in Leads II, IVR, and CR_5, and a low T_3. There was slight coving of the S-T segment in Lead I. No other abnormalities were noted.

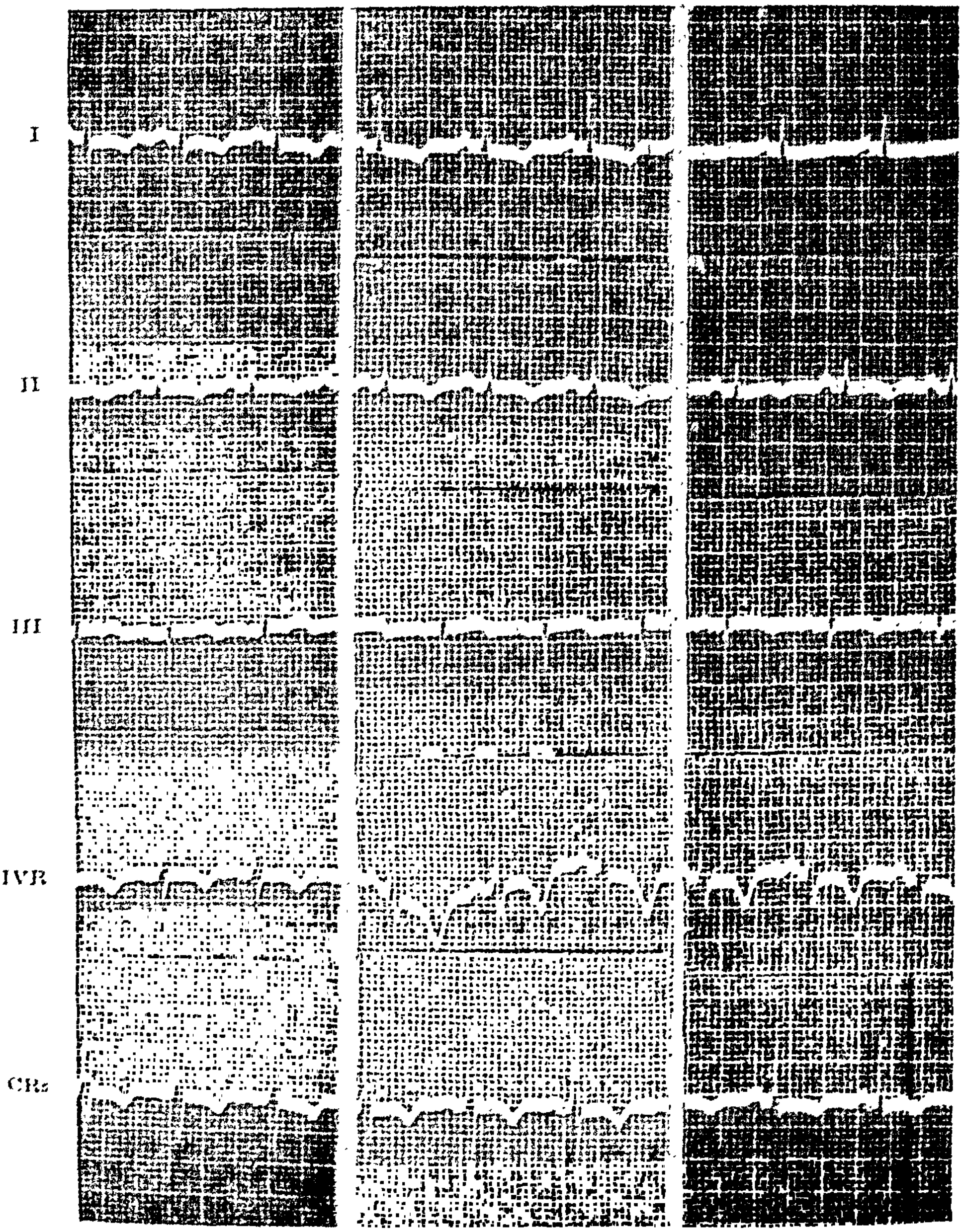

Fig. 1. Fig. 2. Fig. 3.

Figs. 1, 2, and 3.—Electrocardiograms from patient with trichinosis heart disease, at the onset, revealing definite evidence of myocardial damage. Discussed in text. Fig. 1, Feb. 17, 1942; Fig. 2, Feb. 26, 1942; and Fig. 3, March 4, 1942.

Another, taken nine days later (Fig. 2), revealed changes similar to those in Fig. 1, with the exception that the S-T segment in IVR showed definite coving.

In the third electrocardiogram (Fig. 3) there were changes suggestive of healing. T_1 had started to recede, as had the T wave in Lead CR_5. The T waves in Lead III were negative, and the coving of the S-T segment in Lead IVR persisted.

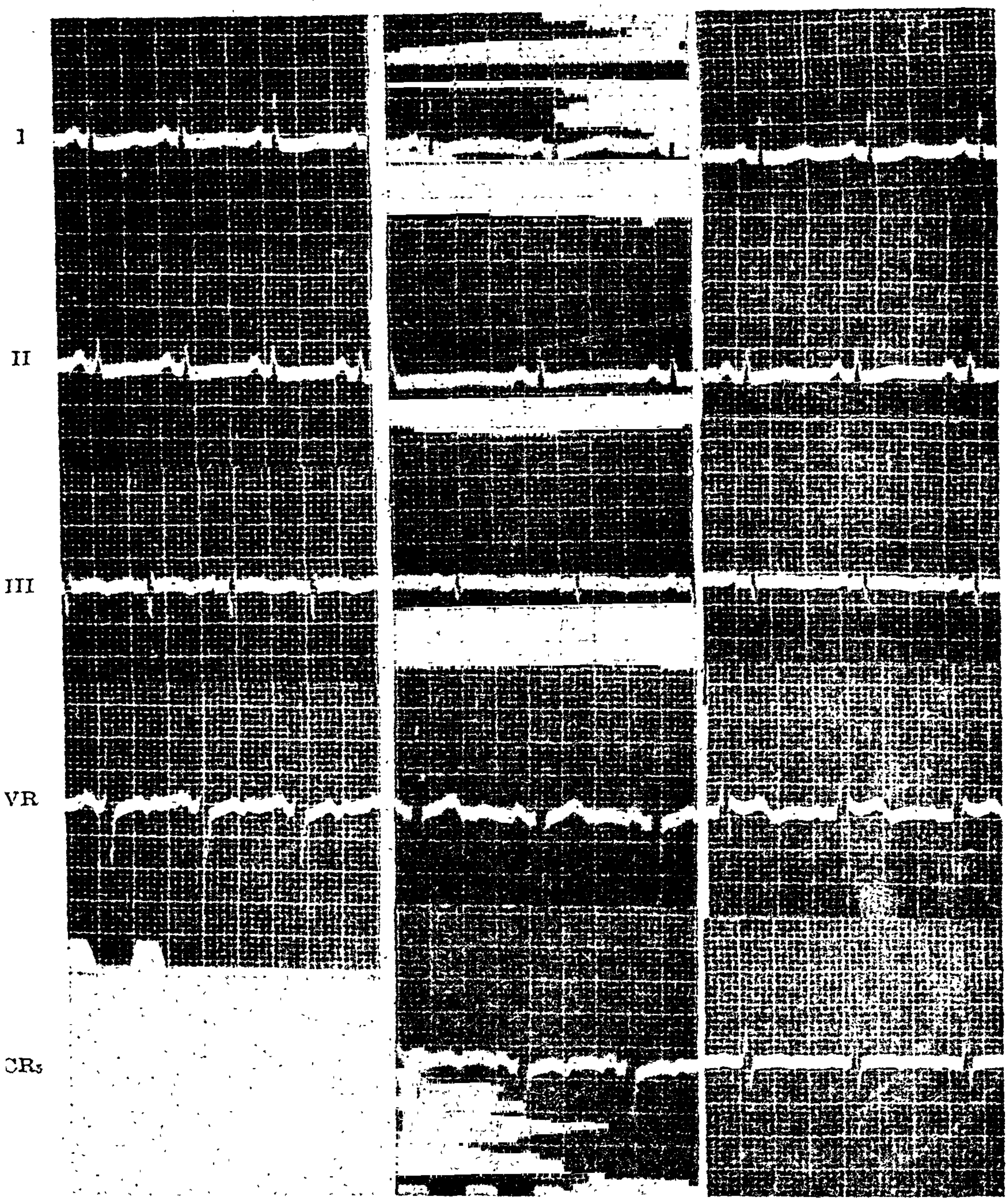

Fig. 4. Fig. 5. Fig. 6.

Figs. 4, 5, and 6.—Electrocardiograms from patient with trichinosis heart disease, showing signs of healing. Discussed in text. Fig. 4, May 7, 1942; Fig. 5, June 4, 1942; and Fig. 6, Oct. 20, 1942.

The subsequent figures showed gradual return of the T waves to the isoelectric line in all the standard leads. The persistent flatness of the T waves in the standard leads and the inverted T waves in IVR and CR_5 after an eight-month period would indicate residual myocardial damage.

The teleoroentgenogram showed a slight increase in the transverse diameter of the heart, probably because of the short stature of the

patient. Radiographic soft tissue studies of the lower part of the legs and the upper part of both arms demonstrated no evidence of encysted trichinae.

Laboratory Examination.—Bone marrow obtained by sternal puncture revealed the following: Many mature polymorphonuclear leucocytes, a profusion of eosinophiles in all stages of development, a slightly increased number of plasma cells, and a normoblastic series which was normal in distribution and maturation.

Biopsy of the left gastrocnemius showed extensive inflammatory infiltration with many eosinophiles and leucocytes. No parasites were found. The inflammatory reaction was suggestive of trichinosis.

Subsequent Course.—The patient has been seen every four weeks since the date of her discharge. Her only complaint has been occasional nervousness and cough. The heart on all occasions has been regular, with a rate of 88 to 90, and the blood pressure remains at approximately 130/90. No murmurs are present. Another cutaneous test for trichinosis was positive. The electrocardiographic changes are illustrated in the accompanying figures.

COMMENT

Medical literature leaves little doubt that the myocardium is resistant to the trichinella organisms. As early as 1860, Zenker[11] first observed the larvae in the myocardium of a patient who had died of the disease. Since that time, mention has been made of the fact by numerous observers, including Frothingham,[12] Prym,[13] Graham,[14] and Zoller.[15] Zoller, who worked with guinea pigs, confirmed the work of Graham,[14] and observed that the larvae were rarely found in the myocardium after the second week of the infection. He concluded that the larvae either were killed in situ or left the myocardium rapidly, re-entering the circulation. The damage to the cardiac muscle was only temporary, he stated, for at no time did he find any evidence of permanent alteration of the myocardium.

The theory advanced by Simmonds,[10] in 1919, that the lesions were caused by toxic substances from the trichinae, carried by the blood stream to the heart, was quite conclusively disproved in 1933 by the work of Dunlap and Weller[3] on white rats which were fed trichinous meat, and more recently by Mauss and Otto.[4] Dunlap and Weller state. "The myocardium showed alterative and exudative lesions in all respects comparable to those found in human hearts. Trichinae embryos were found in these foci as early as five days after feeding. After active migration of the larvae had ceased, the myocardium showed no reaction, although encystment of the larvae in skeletal muscle was occurring to a marked degree.

"It is the presence of the larvae in the myocardium and their active migration, not a blood-borne toxic substance, which produces the charac-

teristic carditis. It is not quite clear what are the factors probably inherent in the heart muscle which prevent encystment."

Mauss and Otto[4] state that the larvae invade the myocardium of rats and are destroyed in situ. Few inflammatory foci suggestive of the presence of worms were seen in the myocardium on the twelfth to fourteen day.

Reports on the electrocardiographic changes caused by trichinella invasion of the myocardium have been to date rather uniform. Masters and Jaffe[16] report a prolonged P-R interval (0.22 second, maximum) and inversion of the T waves. Spink[1, 2] says that T-wave changes occur, especially in Lead II, and are accompanied by low amplitude of the QRS. Cushing[9] reports inversion of T_2 and T_3, and Graybiel and White[17] agree with Masters and Jaffe.[16]

The electrocardiographic changes undoubtedly vary decidedly with the amount of damage inflicted upon the myocardium at any one time, thus eliminating a pathognomonic electrocardiographic alteration. This was true in our case, in which there were T-wave changes in all standard leads and in precordial Leads IVR and CR_5. The P-R interval was never over 0.16 second and the QRS interval never over 0.04 second. The QRS complex approached low voltage in the standard leads. The first two electrocardiograms, taken on the eleventh and thirteenth hospital days, respectively, showed sinus tachycardia. Left axis deviation was present in all the electrocardiograms.

SUMMARY

A case of trichinosis, with infestation of the heart and electrocardiographic changes suggestive of marked myocardial damage, is reported.

The electrocardiographic abnormalities are not always limited to T-wave changes in Leads II and III and prolongation of the QRS complex, but may include T-wave changes in the precordial leads which simulate those which occur in myocardial infarction.

Deviations of the electrocardiogram from normal are dependent upon the amount of damage inflicted upon the myocardium by the trichinellae. The damage undoubtedly varies with the number of invading organisms.

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Abstracts and Reviews

Selected Abstracts

Katz, L. N., Rodbard, S., and Meyer, J.: Blood Pressure Responses of Dogs to Vitamin A and Vitamin D$_2$. Am. J. Physiol. **140**: 226, 1943.

The authors cannot confirm the observations that vitamin A in large quantities lowers the blood pressure in hypertensive dogs; or that vitamin D in large quantities raises the blood pressure in normotensive dogs.

However, it was found that, on occasion, a dog will show a slight lowering of an elevated blood pressure with vitamin A concentrate in fish oil or sesame oil, and a moderate rise in blood pressure with vitamin D. Attention is drawn to the frequent occurrence of a moderate rise in blood pressure of fairly long duration which occurs after a latent period following cessation of vitamin A concentrate therapy.

AUTHORS.

Landsteiner, E. K., and Hayes, M.: The Effect of Temperature of the Blood on the Heart Rate. Am. J. Physiol. **140**: 256, 1943.

In the intact cat and rabbit, the injection of cool physiologic saline solution (22° C. to 36° C.) into the external jugular vein results in a bradycardia, and, conversely, the injection of warm saline solution (43° C. to 57° C.) into the external jugular vein results in a tachycardia. This effect is not altered by bilateral cervical section of the vagus nerves, nor by the action of the several types of anesthetic agents employed.

AUTHORS.

Cossio, P., Dambrosi, R. G., and Bottazzi, J. J.: The Unfolding of the First Sound of the Heart. Rev. argent. de cardiol. **10**: 1, 1943.

The simultaneous records of the phonocardiogram (electric method with selective microphones for different frequencies) with the venous pulse, central arterial pulse, or electrocardiogram, in fifty patients selected at random, presenting at auscultation a reduplication of the first sound, revealed that the reduplication was systolic in forty-one (82 per cent) and presystolic in nine (10 per cent).

In 61 per cent of the cases with systolic reduplication, the two components had the same tonality and practically the same duration, and in 39 per cent, the second component of the reduplication was sharper and shorter than the first, taking the characteristics of a click. In the first type the second component appeared between 0.60 to 0.08 seconds after the beginning of QRS, and coincided with the ascendant limb of the main wave of the central arterial pulse, but in the second type it appeared delayed (sometimes coinciding with a notching in the arteriogram).

In the presystolic reduplication, the first component was made up of vibrations of a lesser frequence, and, generally, not as broad as the second one. Almost always, it was observed in patients with P-Q interval lasting more than 0.20 second. In 20 per cent, it was a simple splitting; in the remaining 80 per cent, a reduplication; both types were better heard and recorded at the apex.

Out of the fifty patients, only 20 per cent had no organic cardiovascular disease, and in every one of them the reduplication happened to be systolic. The rest had systemic or pulmonary hypertension, aortic diseases, or abnormal ventricular activation.

In opposition to what was previously found by the authors, using the direct method of optical recording, in this work the presystolic reduplication of the first sound appeared less frequently than the systolic one, and had always a pathologic meaning, being observed when there were favorable conditions to the appearance of the auricular sound, whether due to prolongation of the A-V conduction time, or to the increase of the diastolic remainder.

The systolic reduplication of the first sound may be due to ventricular asynchronism, or abnormal splitting of the isometric and ejective components, the latter being able to acquire all the characteristics of a click, owing to structural or hemodynamic alterations.

AUTHORS.

Gilligan, D. R., Altschule, M. D., and Katersky, E. M.: Physiological Intravascular Hemolysis of Exercise. Hemoglobinemia and Hemoglobinuria Following Cross-Country Runs. J. Clin. Investigation 22: 859, 1943.

Studies of intravascular hemolysis, as measured by the appearance of hemoglobinemia and hemoglobinuria, have been made in groups of athletes following cross-country runs of 2.6 to 26.2 miles. The plasma bilirubin, the red fragility, the hematocrit, and the urinary albumin and sediment were also studied.

Hemoglobinemia was observed in five of eleven young athletes who ran 2.6 to 2.8 miles, in five of eleven athletes who ran 4.5 to 5.1 miles, and in eighteen of twenty-two men who ran 26.2 miles.

Hemoglobinuria was observed in one of these athletes on three occasions after five-mile runs. Hemoglobinuria occurred in four of the twenty-two men who ran 26.2 miles; these urines were brownish to very dark burgundy red. Observations on one of these four athletes showed the occurrence of hemoglobinuria again after a 20-mile run.

The occurrence of intravascular hemolysis appeared to be unrelated to the age, body build, or standing position of the runners, or to the number of years or state of their training.

Hemoglobinemia and hemoglobinuria disappeared in a few hours after the end of the run. It has been calculated that the amount of blood destroyed intravascularly is very small.

The plasma bilirubin was distinctly elevated after the marathon run. The significance of this hyperbilirubinemia is discussed.

Quantitative studies revealed normal erythrocyte fragility after the marathon runs.

Transient albuminuria was observed frequently after the 2.6- to 5.1-mile runs and in every instance after the marathon run. Transient urinary excretion of formed elements occurred frequently after the shorter runs and in almost every instance after the marathon runs.

Hemoglobinemia sometimes accompanied by hemoglobinuria occurs in man with sufficient frequency after strenuous runs to be considered physiologic under these conditions. This intravascular hemolysis after strenuous runs is comparable in its apparently benign nature to the albuminuria of exercise. The importance of differentiating this condition from pathologic states leading to the passage of red urine is obvious.

AUTHORS.

Wintrobe, M. M., Alcayaga, R., Humphreys, S., and Follis, R. H., Jr.: Electrocardiographic Changes Associated With Thiamine Deficiency in Pigs. Bull. Johns Hopkins Hosp. 72: 169, 1943.

Thiamine deficiency is associated with pronounced electrocardiographic changes in the pig. These include bradycardia and prolonged P-R interval as well as second degree auriculoventricular block, abnormalities in the P waves, inversion of T_4, nodal and ventricular premature beats, auriculoventricular dissociation, complete block with ectopic ventricular rhythm, and auricular fibrillation.

Inanition alone may cause bradycardia but thiamine deficiency appeared to cause a greater degree of slowing than could be accounted for by inanition. It is concluded that, in the thiamine-deficient pig, bradycardia is attributable to the vitamin deficiency rather than, or in addition to, inanition. Evidence is presented which indicates that the bradycardia as well as certain other signs are the result of vagal overaction.

The electrocardiographic changes are probably the expression of the disturbance in metabolism which is caused by lack of thiamine.

AUTHORS.

Dressler, W.: A Case of Myocardial Infarction Masked by Bundle Branch Block but Revealed by Occasional Premature Ventricular Beats. Am. J. M. Sc. 206: 361, 1943.

A case is reported in which myocardial infarction was associated with left bundle branch block. Significant electrocardiographic changes suggestive of myocardial infarction were absent in the regular beats but were displayed by premature beats of ventricular origin.

AUTHOR.

Lascano, E. F.: The Normal Blood Supply of the Node of Tawara, The Bundle of His and Its Branches. Rev. argent. de cardiol. 10: 23, 1943.

By means of injecting the coronaries with a colored gelatin mixture the following has been shown in the human heart:

The first posterior perforating or ramus septi fibrosi of Hass, is the main artery to both the bundle of His and Tawara's node; it anastomoses with others, including quite frequently the one which supplies the sinoauricular node.

In so far as the blood supply to the right branch of the bundle is concerned, this can be divided into three parts. The first is supplied by an anastomotic plexus derived from terminal branches of ramus septi fibrosi, the second posterior perforating (ramus septi ventriculorum superior of Hass), ramus cristae supraventricularis (which runs in the portion of the cardiac muscle so named), and the first anterior perforating arteries. The second part is supplied by the artery to the ansiform band or Gross' ramus limbi dextri, a series of arterioles arising from the plexus supplying the first portion, collaterals of other anterior perforating, and collaterals of posterior perforating arteries. All these vessels anastomose with one another. The third part is supplied by nutrient arteries of the nonspecific myocardium further on than the anterior papillary muscle, which also freely anastomose with one another.

Similarly, the left branch of the bundle of His may be divided, in so far as its blood supply is concerned, into three parts. The first portion is supplied by a plexus of anastomoses formed by the following: terminal branches of the ramus septi fibrosi, terminal branches of ramus septi ventriculorum superior, terminal branches

of ramus cristae supraventricularis, terminal branches of special anterior perforating which was manifest in 50 per cent of the specimens and which the authors propose denominating ramus limbi sinistri, the remaining 50 per cent being supplied by multiple small arterioles. The second part, spreading over the middle and lower parts of the interventricular septum, is supplied by other anterior and posterior perforating arteries which anastomose with one another profusely. The third part is supplied by arteries of the nonspecific extraseptal myocardium which also freely anastomose with one another.

By means of improvements in the classic techniques of investigating coronary circulation and performing various experiments, it was possible to demonstrate definitely and clearly that not only do the arteries intrusted with the blood supply to the node (Tawara's), bundle of His, and its branches, anastomose with one another, but that *these same vessels do so with the nutrient arteries of the nonspecific* myocardium. These arteries should be considered as merely main arteries and not terminal vessels to the above-named node, bundle, and its branches. The anastomoses have a diameter of roughly 50 microns, and, from the abundant number of vessels involved, it can be deduced that these anastomoses play an important function.

Both the main arteries and the anastomoses concerned in the supply to Tawara's node, the bundle of His, and its branches, run in the same direction as the wave of excitability.

AUTHOR.

Jaleski, T. C., and Morrison, E. T.: Congenital Heart Block: A Study of Two Cases in Healthy Adults. Am. J. M. Sc. **206:** 449, 1943.

Two cases of congenital heart block are reported. The first case, which has been studied for four years, is a healthy adult who has no cardiac symptoms and no other apparent anomalies. The second case, which has been followed from birth, has had no cardiac symptoms except for some syncopal attacks. This case is of particular interest in that the patient has had two normal pregnancies without any serious cardiac disturbance.

AUTHORS.

Luisada, A. A., and Mautner, H.: Experimental Studies on Functional Murmurs and Extra Sounds of the Heart. Exp. Med. & Surg. **1:** 282, 1943.

Experimental studies have been made on heart sounds and murmurs of animals with simultaneous registration of the electrocardiogram and the phonocardiogram. Different drugs have been injected, the vagus nerve stimulated, and other procedures also tried in order to produce extra sounds and murmurs.

Analysis of the records has shown the following results: A systolic murmur is often present in marked tachycardia, independently from pressure conditions. Prolongation of the heart sounds because of bundle branch block may simulate murmurs. Extra sounds, causing the appearance of gallop rhythm, occur in certain experimental conditions where vagus stimulation is accompanied by increased contractility of the myocardium. During heart block two loud sounds may follow a blocked auricular contraction. A prolonged auricular sound and also a prolonged third sound may be observed in some experimental conditions. Sometimes they may attain such length as to become real functional rumbles. Possible explanations are discussed. Unexplained extra sounds were observed exceptionally, and are discussed in the text.

AUTHORS.

Rich, A. R., and Gregory, J. E.: Experimental Evidence That Lesions With the Basic Characteristics of Rheumatic Carditis Can Result From Anaphylactic Hypersensitivity. Bull. Johns Hopkins Hosp. 73: 239, 1943.

Rabbits subjected to experimental serum sickness develop, in some cases, cardiac lesions that, in their basic characteristics, resemble closely those of rheumatic carditis. These lesions are illustrated, and circumstances compatible with the view that the lesions of rheumatic fever may be the results of focal reactions of the anaphylactic type are discussed.

AUTHORS.

Banerjea, J. C.: Subcutaneous Nodules in Rheumatism. Indian J. Pediat. 10: 41, 1943.

The Indian literature on the incidence of rheumatic infection, rheumatic heart disease, and rheumatic nodules has been reviewed. A clinical study on rheumatic nodules based on 181 cases of juvenile rheumatism has been presented.

The incidence of rheumatic nodules is 8.2 per cent. From a comparison of the corresponding figures of different workers in different countries, it appears that acute rheumatism in Bengal, if not in India, follows closely that in the temperate zones, namely, Europe, and the United States. Its essential clinical features, including the occurrence of subcutaneous rheumatic nodules, are also similar.

AUTHOR.

Dressler, M., and Silverman, M.: Cardiovascular Syphilis: An Approach to Early Clinical Recognition and Early Treatment. Ann. Int. Med. 19: 224, 1943.

Of 1,270 cases of proved syphilis studied, 24 per cent were diagnosed clinically as uncomplicated aortitis, and 30.7 per cent as cardiovascular syphilis as a whole. Of the latter group, 78 per cent were cases of uncomplicated aortitis. The proportion of males to females was approximately two to one, and that of the white to the Negro race approximately the same.

The criteria for the physical diagnosis of uncomplicated aortitis are presented and discussed, and are found of value in patients 40 years of age or younger. It is more common in the Negro than in the white race in this age group. The high percentage (47.4 per cent) of hypertension among the cases of cardiovascular syphilis studied is not purely coincidental. No valid reason is advanced for its presence. Uncomplicated aortitis is more common among congenital syphilitics than has been reported heretofore.

Of 128 patients with cardiovascular syphilis who remembered the chancre, uncomplicated aortitis had been diagnosed in thirty-eight cases within ten years after the primary infection. Uncomplicated aortitis is a symptomless disease. Hints on physical diagnosis are discussed. Neurosysphilis was present in 26.6 per cent of the cases of cardiovascular syphilis. Fluoroscopy and roentgenography are of value in corroborating the clinical diagnosis. Uncomplicated aortitis can be diagnosed clinically in a normal-sized aorta.

AUTHORS.

Golden, A., Dexter, L., and Weiss, S.: Vascular Disease Following Toxemia of Pregnancy (Preeclampsia and Eclampsia); Observations on Its Clinical Course. Arch. Int. Med. 72: 301, 1943.

The rather common occurrence of permanent vascular disease following toxemia of pregnancy (pre-eclampsia and to a less extent eclampsia) is described, and the clinical course of this hypertension is studied.

The clinical analogy between toxemia of pregnancy and acute glomerulonephritis as regards the acute phases and the late effects on the vascular system is pointed out.

The duration, more than the severity, of the toxemia during pregnancy determines the development of permanent post-partum vascular disease.

A latent period of at least several months may intervene between toxemia of pregnancy and the development of recognizable permanent hypertension or albuminuria.

After toxemia of pregnancy, hypertension may persist for at least a year and then disappear.

The post-partum course may be predominantly hypertensive or albuminuric, apparently dependent on a similar predominance in pregnancy.

The course is prone to be rapidly progressive in comparison with that of the other types of hypertension.

Death usually occurs as a result of uremia, cardiac failure, or cerebral hemorrhage, as in other types of hypertension. Retinal changes occur, such as vascular sclerosis, hemorrhages, and exudates, but no instances of true albuminuric retinitis have been observed.

Nephrosclerosis is the characteristic post-mortem finding. The pathologic condition in the kidneys in other respects is variable, however, and at times may duplicate that of chronic glomerulonephritis. This is not surprising, as both diseases start with a diffuse glomerular lesion, and the hypertensive vascular disorders following the two diseases may run almost identical clinical courses.

The importance of recognizing this group of patients with posttoxemic hypertension lies in its prevention. The late vascular effects of toxemia may be prevented by interrupting pregnancy before hypertension and albuminuria of toxemia have lasted for more than three weeks. This applies as much to mild as to severe toxemia.

AUTHORS.

Likoff, W. B., and Levine, S. A.: Thyrotoxicosis as the Sole Cause of Heart Failure. Am. J. M. Sc. 206: 425, 1943.

A study was made of 409 cases of thyrotoxicosis operated upon at the Peter Bent Brigham Hospital, from 1923 to 1941, inclusive. There were 331 (81 per cent) "noncardiacs" and 78 (19 per cent) "cardiacs." Among the latter there were 45 with hypertensive disease, 20 with rheumatic heart disease, 12 with coronary artery disease, and one with syphilitic aortic insufficiency.

There were 39 cases of heart failure among the 78 "cardiacs" (50 per cent), and 21 instances of definite congestive failure among the 331 "noncardiacs" (6.3 per cent). It is apparent, therefore, that thyrotoxicosis not infrequently is the sole cause of congestive heart failure.

It was found that congestive failure was more likely to occur in the female sex, with increasing age, when the thyrotoxic state lasted longer and when auricular fibrillation was present. No satisfactory explanation was found for the heart failure especially in the "noncardiac" group. It is suggested that vitamin B deficiency may play a contributory part.

The similarity between symptoms and physical findings in mitral stenosis and thyrotoxicosis may lead to errors in diagnosis, for even left auricular dilatation on roentgen ray examination is found in the latter condition.

In 99 cases with cardiac involvement there was no surgical mortality. All but seven of these had a one-stage subtotal thyroidectomy. The surgical mortality in 310 cases without heart disease, however, was 2.6 per cent. It is believed, therefore, that the so-called severe thyrocardiacs require a multiple stage operation, and it is felt that they cause less concern than the younger exophthalmic goiter cases, when surgical treatment is planned.

It is evident that "masked thyrotoxicosis" is being overlooked as a cause of heart failure, an error which is very costly because the condition is curable.

AUTHORS.

Taylor, R. D., Corcoran, A. C., Shrader, J. C., Young, W. C., and Page, I. H.: Effects of Large Doses of a Vitamin A Concentrate in Normal and Hypertensive Patients. Am. J. M. Sc. 206: 659, 1943.

Vitamin A concentrate is ineffective in the treatment of essential hypertension in daily doses of 100,000 to 400,000 units for five to ninety days.

The vitamin concentrate causes renal vasodilatation and increased functional capacity for secretion of diodrast with increased cardiac output. The suggestion is made that it may have application in the treatment of degenerative renal diseases.

AUTHORS.

Howland, E. S., and Sprofkin, B. E.: Saccular Aneurysm of the Abdominal Aorta: Report of a Case With Terminal Anuria and Rupture into the Duodenum. Am. J. M. Sc. 206: 363, 1943.

The recent literature relating to saccular aneurysm of the abdominal aorta (520 cases) has been reviewed with especial reference to cases with rupture into the intestinal tract (fifteen cases) and those associated with symptoms suggesting urologic disease.

A case, apparently of arteriosclerotic origin, is presented in which there was both anuria of three days' duration, and rupture of the aneurysm into the duodenum as a terminal event.

AUTHOR.

Laipply, T. C.: Syphilitic Aneurysm of Celiac Artery. Am. J. M. Sc. 206: 453, 1943.

Review of the literature shows that aneurysm of the celiac artery is rare. The case reported is one of saccular syphilitic aneurysm of the celiac artery complicated by bleeding into the intestinal canal by way of the pancreatic duct. The signs and symptoms simulated acute cholecystitis.

AUTHOR.

McCall, M., and Pennock, J. W.: Disseminated Necrotizing Vascularities—The Toxic Origin of Periarteritis Nodosa. Am. J. M. Sc. 206: 652, 1943.

Widespread necrotizing arteritis is herewith described in a series of autopsies. There was no history of sulfonamide sensitivity or serum sickness in these patients. Sulfonamide therapy was used in the terminal illness. The vascular lesions were widespread, and are considered to be a specific reaction of blood vessels previously sensitized by some nonspecific toxin.

AUTHORS.

Van Dellen, T. R., de Takáts, G., and Scupham, G. W.: Vascular Diseases, Ninth Annual Review. Arch. Int. Med. 72: 518, 1943.

The present review compiled under wartime conditions does not show a noticeable decline in original material during the past year. Dicourmarin has been given considerable attention, and many of the articles on heparin have been omitted, pending decision as to their value when this drug is finally compared with the former compound. The review includes a critical, comprehensive summary of the literature on vascular surgery. This has been focused naturally this year on war injuries and their treatment. A notable feature is a review of the results obtained from ligation of the patent ductus arteriosus in the presence of subacute bacterial endocarditis.

MCCULLOCH.

Gregg, D. E., Pritchard, W. H., Shipley, R. E., and Wearn, J. T.: Augmentation of Blood Flow in the Coronary Arteries With Elevation of Right Ventricular Pressure. Am. J. Physiol. 139: 726, 1943.

The effect of pulmonary artery constriction upon coronary inflow has been studied in the anesthetized open chest dog. Progressive elevation of right ventricular pressure by this means (to 80 mm. Hg systolic) is accompanied by a progressive and considerable augmentation in right coronary inflow (25 to 200 per cent) and a smaller but definite increase in left coronary inflow (19 to 29 per cent) when aortic perfusing pressure remains, or is kept, at the control value. Right coronary inflow may also increase in spite of a moderate, uncompensated reduction in coronary perfusing pressure (aortic pressure).

These findings, obtained in the anesthetized, open chest dog, are diametrically opposed to those reported by other investigators using different methods and preparations.

AUTHORS.

Henderson, Y.: Tonus and the Venopressor Mechanism: The Clinical Physiology of a Major Mode of Death. Medicine 22: 223, 1943.

The author's studies on how men die, made during the past forty years, are summarized. Among the vasomotor and venopressor reactions and adjustments or maladjustments of the circulation, by far the most important is the primary failure in the spinal motor centers. It occurs gradually as the dying patient grows weaker. The muscles lose their tonus and intratissue pressure. The booster pumps in the bundles of muscle fibers beat more and more feebly. Less and less blood is supplied to the right heart and correspondingly less is available to be pumped into the arteries by the left heart. As the arterial stream diminishes, the vasomotor mechanism makes a compensatory effort to maintain sufficient arterial pressure to supply blood to the brain. And when further compensation is no longer possible, the final and fatal fall of arterial pressure and standstill of the circulation occur.

AUTHOR.

Winkler, A. W., and Hoff, H. E.: Potassium and the Cause of Death in Traumatic Shock. Am. J. Physiol. 139: 686, 1943.

Concentration of potassium in serum consistently increases when secondary shock is induced by re-establishment of circulation in an ischemic limb.

Death usually occurs with respiratory failure prior to or simultaneous with cardiac arrest, and is usually not due to potassium poisoning. Concentrations of potassium in serum, while both respiration and heart are active in the shocked animal, seldom exceed 8 mM per liter. These levels are too low to cause any circulatory embarrassment; minor electrocardiographic changes only are noted.

Exceptionally, death may be due to cardiac arrest from spontaneous autointoxication with potassium. Long persistence of the shocked state with failure of renal excretion favors this event. It is characterized by the attainment of concentrations of potassium in serum exceeding 10 mM per liter while both heart and respiration are active, and by cardiac arrest while the respirations are still normally active.

After respiratory arrest, there may be a rapid agonal elevation of the serum potassium. Such increases are the result and not the cause of the terminal event.

AUTHORS.

Lange, K., and Boyd, L. J.: Objective Methods to Determine the Speed of Blood Flow and Their Results (Fluorescein and Acetylene). Am. J. M. Sc. 206: 438, 1943.

The appearance of fluorescein in the lips under a special long-wave ultraviolet light can be used to determine the circulation time, but certain conditions must be observed in order to obtain reliable results.

In 212 normal adults, the values for the fluorescein circulation time ranged between 15 and 20 seconds, and the majority between 15 to 17.5 seconds.

The average of the circulation time is longer in older patients.

Work accelerates the circulation time considerably and may make it two and a half times faster than normal.

Fever shortens circulation time (six cases).

The fluorescein method can be used to determine the velocity to different points of the body. The average time to conjunctiva, lips, rectum, and foot, is 10, 15, 18, and 23 seconds, respectively. The conjunctiva is not an appropriate place to test the circulation time.

In congestive right heart failure, 92 per cent of the cases (123 patients) show a prolonged circulation time, while compensated cases of heart disease have normal circulation times.

Pure bronchial asthma, having a normal or slightly shortened circulation time, can be differentiated by the fluorescein circulation time from cardiac asthma, which has a prolonged circulation time.

Hyperthyroidism is associated with shortened circulation time values, which seems to provide an earlier indication of the clinical situation than the basal metabolic rate.

Patients with hypothyroidism have prolonged circulation times.

Anemia considerably shortens the circulation time when the red blood cell count goes below 3,500,000.

Inhalations of acetylene can be used to determine the time which elapses until all blood in rapid circulation has passed the lungs at least once ("slowest circulation time"). (a) Twenty-four normals had slowest circulation times of 2½ to 3½ minutes. (b) Ten cases of thyrotoxicosis showed slowest circulation times of 1½ to 2 minutes, and patients in cardiac failure had slowest circulation times of up to six minutes. (c) Work shortens the slowest circulation time as much as two and a half times the normal. (d) The comparative values found with the fluorescein method for the fastest, and the acetylene method for the slowest, circulation time show the same relation.

AUTHORS.

Zimmerman, S. L.: Carotid Sinus Syndrome: A Report of Three Additional Cases From the Cardiological Service, U. S. V. A. Facility, Columbia, South Carolina. J. Lab. & Clin. Med. 28: 1548, 1943.

Three cases of carotid sinus syndrome, two of the vagal type and one of the depressor type, are reported. In all, medical treatment afforded some relief. One of the patients with the depressor type had an associated low basal metabolic rate. His response to medication was not reliable, possibly in view of his failure to diligently take the ephedrine. The results with the vagal type cases have been more encouraging.

In all three of these reported caess, the presence of the syndrome was easily established. In two, the history revealed the precipitating factor to be an abnormal or suddn movement of the head or neck. In the third, the patient learned that he could avoid such an attack by holding his head still, between his hands.

The syndrome should be borne in mind in all cases of unexplained syncope, especially if associated with abnormal movements of the head and neck.

AUTHOR.

Battro, A., and Labourt, F. E.: Considerations on the Determination of Maximal Ventilation and Pulmonary Reserve and Hyperpnea of Cardiac Patients. Rev. argent. de cardiol. 10: 83, 1943.

On the basis of observations made in ten normal persons and nineteen pathologic cases, most of whom had congestive cardiac failure, it is concluded that the values of maximal ventilation and pulmonary reserve deduced from the value of the vital capacity, actual or calculated, do not conform with those obtained from direct measurement.

The relation of these measurements to the hyperpnea of cardiac patients was studied.

In those cases in which the pulmonary reserve (maximal ventilation minus minute respiratory volume) was less than 70 per cent of the maximal ventilation, dyspnea and pulmonary congestion were present.

In one case of congenital heart disease with cyanosis and dyspnea, the pulmonary reserve was 82 per cent. In this and similar cases, dyspnea is probably related to blood chemical changes due to the arteriovenous shunt.

Pulmonary reserve diminished in the recumbent posture with the head in a low position and dyspnea increased without great modification of vital capacity. The diminished pulmonary reserve was due to diminution of maximal ventilation and increase of respiratory minute volume.

AUTHORS.

Gregg, D. E., Shipley, R. E., and Bidder, T. G.: The Anterior Cardiac Veins. Their Functional Importance in the Venous Drainage of the Right Heart. Am. J. Physiol. 139: 732, 1943.

The number and anatomic distribution of the major anterior cardiac veins of the dog's heart have been studied from roentgenograms of specimens injected immediately post mortem. Inspection alone reveals that the greater portion of the subepicardial surface of the right ventricle is traversed by many small branches which merge to form, in different hearts, from two to five major anterior cardiac veins. Each major vein empties separately and directly into the right atrium, about 4 to 8 mm. superior to the border of the tricuspid valve. Other smaller veins are invariably present.

The functional importance of the anterior cardiac veins, virtually ignored by previous investigators, is demonstrated. In sixteen anesthetized open chest dogs with different body weights and blood pressures, the flow from all the major anterior cardiac veins cannulated ranged from 8.5 to 26.5 c.c. per minute. The flow could be increased greatly by various procedures. It was established that flow from the anterior cardiac veins is almost, if not entirely, derived from the coronary arteries, and its magnitude generally approaches and not infrequently exceeds the simultaneously measured right coronary inflow.

The major portion (50 to 92 per cent) of right coronary inflow was found to drain via the anterior cardiac veins into the right atrium. This finding makes completely untenable the conventionally accepted belief that nearly all of the right coronary inflow drains by way of the Thebesian vessels into the right ventricle.

To prevent confusion in terminology for the cardiac veins considered here, it is suggested that the officially accepted name "anterior cardiac veins" (BR of BNA) be used when indicated, and the conventional use of the misleading term "accessory veins," as applied to an aggregate of several unspecified vessels, be avoided.

AUTHORS.

Baila, M. R., and Goñi Moreno, I.: Ligation of the Ductus Arteriosus. Rev. argent. de cardiol. 10: 107, 1943.

A case is reported of persistent ductus arteriosus treated surgically by ligation. The clinical course of eight other nonoperated cases is described and the indications of the surgical treatment are discussed. The authors consider that ligation of the persistent ductus should be made only in those cases in which the congenital defect causes marked physical disability.

AUTHORS.

Crismon, J. M., Crismon, C. S., Cababresi, M., and Darrow, D. C.: Electrolyte Redistribution in Cat Heart and Skeletal Muscle in Potassium Poisoning. Am. J. Physiol. 139: 667, 1943.

Heart, skeletal muscle, and serum electrolytes and water analyses were made on twenty-three cats in which the electrocardiograph was used to detect potassium poisoning.

Potassium poisoning, as judged from the disappearance of P waves from the electrocardiogram, occurred when the serum potassium reached 11.0 meq. per liter, but was detected in some cases at lower serum concentrations if the rate of rise of potassium was faster than 0.33 meq. per liter per minute.

No quantitative relationship could be demonstrated between the amount of potassium found in the heart and the appearance of potassium poisoning, although both the heart and skeletal muscle were found to take up potassium readily if the plasma concentration is elevated.

The uptake of potassium by the heart is associated with the loss of sodium and the appearance of considerable quantities of chloride in the intracellular phase.

The above observations are discussed in relation to their significance in potassium poisoning.

AUTHORS.

Hiatt, E. P.: The Action of Adrenaline, Acetylcholine and Potassium in Relation to the Innervation of the Isolated Auricle of the Spiny Dogfish (Squalus Acanthias). Am. J. Physiol. 139: 45, 1943.

The isolated sinus-auricle preparation of the elasmobranch *(Squalus acanthias)* which is apparently without sympathetic innervation, shows marked reactions to adrenalin.

The previously reported observation that adrenalin in high concentration causes a transient inhibition has been confirmed, but this effect is not blocked by atropine, so it is concluded that the action is not upon the vagus endings as has been suggested, but that it is directly upon the myocardial cells.

Adrenalin in low, more nearly physiologic concentrations causes augmentation of the contractions without a change in rate. This effect also persists after atropine.

The dogfish auricle is much more resistant to the action of acetylcholine in the absence of an inhibitor of choline esterase than the auricles of frog and turtle hearts, but after treatment with prostigmine the dogfish auricle reacts in the same manner and with approximately the same sensitivity as other vertebrate auricles to acetylcholine.

The inhibitory actions of acetylcholine and the depression of auricular beat due to potassium excess are markedly antagonized by small concentrations of adrenalin.

A possible teleologic value of the sensitivity of the myocardial cells to adrenalin is suggested.

AUTHORS.

Levinson, J. P., and Essex, H. E.: Observations on the Effect of Certain Drugs on the Small Blood Vessels of the Rabbit Ear Before and After Denervation. Am. J. Physiol. 139: 423, 1943.

A study of the reactions of the minute blood vessels seen in the transparent chambers inserted in the ears of albino rabbits has been presented. The response of these blood vessels to epinephrine, ephedrine, pitressin, and ergotoxine has been recorded for innervated and denervated ears. Observations were also made on the effect of stimulation of the auricular and cervical sympathetic nerves on these blood vessels. Each animal was grossly examined at necropsy for evidence of regeneration of nerves.

The following conclusions were drawn:

The tissue grown into a transparent chamber inserted in the rabbit's ear is entirely suitable for physiologic studies.

The response to epinephrine was a consistent constriction of the arterioles accompanied by slight narrowing of the venules.

Ephedrine, in general, produced the same response as epinephrine. There was evidence of refractoriness to repeated doses of ephedrine.

Pitressin in the dose used (0.1 pressor unit per kilogram of body weight) had the most pronounced vasoconstrictor action. There was, as with ephedrine, refractoriness to repeated doses of pitressin.

Ergotoxine blocked the vasoconstrictor action of epinephrine.

Stimulation of the cervical sympathetic chain produced a constriction of the arterioles in the window more consistently than did stimulation of the dorsal or great auricular nerves.

The denervated vessels in the chamber became hypersensitive to epinephrine and regained their "tone" after denervation. Suggestions have been made as to the mechanism involved.

The blocking action of ergotoxine and the phenomenon of tachyphylaxis are apparently somewhat altered by denervation.

AUTHORS.

Chen, K. K., and Steldt, F. A.: Cerberin and Cerberoside, the Cardiac Principles of Cerbera Odallam. J. Pharmacol. & Exper. Therap. 76: 167, 1942.

Cerberin can be isolated from both the oil and the defatted kernels of *Cerbera odallam* nuts.

From a second batch of nuts, a glycoside similar to but not identical with cerberin has been isolated, to which the name of cerberoside has been proposed.

Both cerberin and cerberoside have a digitalis-like action. Cerberin is much more potent on the heart than cerberoside.

AUTHORS.

Sokolow, M., and Chamberlain, F. L.: Clinical Evaluation of Cedilanid. Ann. Int. Med. 18: 204, 1943.

Lanatoside C (cedilanid) is a pure, stable, crystalline glycoside derived from *Digitalis lanata*. It is a potent therapeutic agent in congestive cardiac failure with normal rhythm, in auricular fibrillation, and in auricular flutter. In auricular fibrillation, intravenous cedilanid produces an abrupt fall in the ventricular rate, frequently within ten minutes.

The average oral digitalizing dose of cedilanid is 7.5 mg. in three days. The average intravenous digitalizing dose is 8 c.c. (1.6 mg.) in twenty-four hours. The average maintenance dose of oral cedilanid is 1.6 mg.

Oral cedilanid apparently is absorbed three times as readily as oral *Digitalis purpurea*. This is based on the fact that the digitalizing dose of cedilanid is only

4.7 times its maintenance dose whereas the digitalizing dose of *Digitalis purpurea* is 11.3 times its maintenance dose.

No striking difference in clinical effects was noted between oral cedilanid and oral *Digitalis purpurea*.

The most important therapeutic advantage of cedilanid is obtained from the intravenous preparation, primarily because of its rapid action. Approximately 2.8 times as much drug is required for oral as for intravenous twenty-four-hour digitalization.

AUTHORS.

Klein, C., Saland, G., and Zurrow, H.: Pancreatic Tissue Extract (Insulin-Free) in the Treatment of Peripheral Vascular Disease. Ann. Int. Med. 18: 214, 1943.

Pancreatic tissue extract, insulin-free, produced a drop in the muscle temperature of the lower extremity, with no significant effect on the skin temperature, when injected intramuscularly.

Pancreatic tissue extract, insulin-free, had no effect on claudification time, as measured by ergometer, within one-half hour of intramuscular injection.

Pancreatic tissue extract, insulin-free, injected intramuscularly in 3 c.c. doses twice a week for relatively long periods of time, from six to eighteen months, produced improvement in claudication time and rest pain.

Pancreatic tissue extract, insulin-free, injected intramuscularly in 3 c.c. doses twice a week for relatively long periods of time, from six to eighteen months, had no effect on vascular anatomic or tissue anatomic status, on vascular reserve, or on functional classification.

Patients receiving no specific treatment but following instructions concerning hygienic care of the feet, showed a definite degree of improvement in vascular reserve, as measured by thermal test or nerve block.

AUTHORS.

Plentl, A. A., Page, I. H., and Davis, W. W.: The Nature of Renin Activator. J. Biol. Chem. 147: 143, 1943.

An electrophoretic analysis of hog serum has been made which showed the presence of five distinct proteins. α-Globulin was found to exhibit the phenomenon of a double peak. The serum was fractionated by precipitation with ammonium sulfate, which yielded some of the globulins in reasonably pure form. α- and γ-globulins were found to precipitate within the concentration limits reported for horse serum, but the limits for albumin were found to be much higher. β-Globulin could not be obtained in pure state. Pseudoglobulin fractions were incubated with various amounts of renin and only the α_2-globulin component found to act as substrate for the production of angiotonin. Euglobulins were entirely inactive. The relative efficiency of serum, activator, and α-globulin as substrate was compared and the amount of angiotonin formed was found to be proportional to the concentration of α_2-globulin. The substance referred to as renin activator is therefore identical to, or moves with the same electrophoretic mobility as α_2-globulin.

An appreciable quantity of angiotonase has been demonstrated in the albumin fraction, while none could be found in the globulins.

AUTHORS.

Raab, W.: Epinephrine and Related Substances in Human Arterial Walls and Kidneys: Their Role in Arteriosclerosis. Arch. Path. 35: 836, 1943.

Epinephrine and epinephrine-like substances (adrenal catechols) were determined colorimetrically in human aortas, renal arteries, and kidneys.

Infantile tissues contained the lowest total amounts of chromogenic material. It consisted almost entirely of epinephrine proper or sympathin.

With advancing age, increasing amounts of other, epinephrine-like substances, similar to those produced by the adrenal medulla, were found to accumulate in vascular walls and kidneys.

Abnormally large concentrations were observed in the vessels and the kidneys of persons with adrenal tumors.

Sclerotic aortas contained high concentrations of chromogenic material other than epinephrine proper more frequently than normal aortas.

In arteriosclerotic kidneys, on the other hand, pure epinephrine or sympathin was more commonly encountered than in morphologically normal kidneys. In this respect arteriosclerotic kidneys resemble the failing hypertrophic and damaged human heart.

In cases of marked albuminuria the renal concentrations of the total chromogenic material or of epinephrine proper were high.

The role of adrenal hormones and sympathin as intrinsic damaging agents in the origin of arteriosclerosis is discussed.

AUTHOR.

Hueper, W. C.: Experimental Studies in Cardiovascular Pathology. VII. Chronic Nicotine Poisoning in Rats and in Dogs. Arch. Path. 35: 846, 1943.

Rats and dogs given subcutaneous injections of nicotine over eight to ten months were found to have degenerative lesions in the elastic and muscular arteries and arterioles. The morphologic type of arterial changes produced reflects the nature of the mechanism of action of nicotine (vasoconstrictive ischemic noxemia).

Female rats given injections of nicotine only, and male rats given injections of nicotine and epinephrine, nicotine and desoxycorticosterone acetate, and nicotine and mecholyl chloride, respectively, showed a much higher mortality rate than male rats receiving nicotine only, particularly male rats given injections of nicotine and kept on a diet containing additions of cystine and ascorbic acid.

Exogenous and, possibly, dietary factors may account in part for the differences in individual susceptibility to nicotine in man and in animals.

The testicular degenerations occurring in an appreciable number of rats treated seemed to be the result of vasoconstrictive episodes of anoxemia.

AUTHOR.

Boyd, L. J., and Scherf, D.: Magnesium Sulfate in Paroxysmal Tachycardia. Am. J. M. Sc. 206: 43, 1943.

The effect of intravenous injections of magnesium sulfate in ten cases of paroxysmal tachycardia and one case of flutter was studied.

The injection of a 10 per cent solution was beneficial in three out of eight attacks, while a 20 per cent solution succeeded in eight out of eight attacks. Consequently the use of a 20 per cent solution is advocated.

Disturbances of conduction and ventricular extrasystoles appear for a short time after the injection. The rate of paroxysmal tachycardia frequently diminishes before the tachycardia disappears.

In the doses and with the indications discussed, the intravenous injection of magnesium sulfate may be recommended as a useful therapeutic procedure in paroxysmal tachycardias.

AUTHORS.

Ranges, H. A., and Bradley, S. E.: Systemic and Renal Circulatory Changes Following the Administration of Adrenin, Ephedrine, and Paredrinol to Normal Man. J. Clin. Investigation 22: 687, 1943.

A study of systemic and renal circulatory changes in thirty-one normal subjects during the action of adrenin, ephedrine, and paredrinol, has been reported. Cardiac output has been measured by the ballistocardiograph, arterial pressure with the Hamilton manometer, and right intra-auricular pressure, following catheterization of the right heart, with a saline manometer. Renal plasma flow was determined as diodrast clearance, glomerular filtration rate as mannitol or inulin clearance, and the filtration fraction as the mannitol/diodrast ratio.

Adrenin and ephedrine were found to display similar activity. Evidence was adduced to support the view that the vasodilator action of these substances dominated the hemodynamic picture with an increase in cardiac output, associated with increased intra-auricular pressure, producing the pressor effects. Increased pulse pressure, without corresponding increases in stroke volume or cardiac output, indicated a direct action of these drugs upon the central arteries.

Paredrinol has proved to be a predominantly vasoconstrictor drug with its primary site of action in the periphery. Peripheral resistance and blood pressure rose, and cardiac output declined, in the face of increased right auricular pressure. It was inferred that paredrinol increased cardiac tone.

All the substances studied produced identical renal effects. Renal plasma flow decreased without significant change in the glomerular filtration rate and the filtration fraction increased, indicating efferent arteriolar vasoconstriction.

AUTHORS.

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**Executive Committee.*

American Heart Journal

Vol. 27 | March, 1944 | No. 3

Original Communications

THE EFFECT OF CERTAIN SUBSTANCES ON THE INTRAHEPATIC CIRCULATION OF BLOOD IN THE INTACT ANIMAL

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In a previous study,[1] the distribution and manner of communication of arterial and venous blood within the liver of the intact animal were ascertained by means of the quartz-rod transillumination technique. With the background gained from that work, it seemed advisable to study the effects of various substances, such as glucose, dyes, particulate matter, thyroxin, epinephrine, and acetylcholine, on the intrahepatic circulation of blood in the intact animal by the same method—especially since the literature on the subject revealed a lack of agreement among investigators who had studied by various methods the effects of these substances on the intrahepatic circulation.

METHODS

For studying the effects of various substances on the intrahepatic circulation, the quartz-rod transillumination technique was employed. The frog (*Rana pipiens*) and the albino rat (*Rattus norvegicus*) were the animals used. The observations on the frog were made at room temperature, but those on the mammal were made at animal body temperature by the use of a constant temperature apparatus. The administration of the anesthetic agent, the preparation of the animals, and the exposure of the liver were performed in the manner described in a previous study of the intrahepatic circulation.[1] For fear that the acetylcholine, epinephrine, or glucose might deteriorate on standing, the solutions were prepared freshly before administration.

EPINEPHRINE

Literature.—Fröhlich and Pollak[2] stated that neither concentrated nor dilute solutions of epinephrine have any constrictor effect on the

This work was done at the Institute of Experimental Medicine, Mayo Foundation, Rochester, Minn. The author wishes to thank Dr. Frank C. Mann for his interest and helpful suggestions.

Received for publication May 3, 1943.

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portal ramification in the frog's liver. Morita[3] found that a 1:200,000 solution of epinephrine did not have any influence on the caliber of the portal capillaries within the liver. Wertheimer[4] obtained such a sudden and strong effect of epinephrine on the hepatic vessels that the intrahepatic circulation was permanently brought to a standstill, and this could be observed macroscopically. Snyder and Martin[5] stated that the type of reaction of the hepatic vessels of the turtle to epinephrine depends on the pH of the perfusate. Maloff[6] attributed the constriction of the capillaries of the isolated liver of the frog to the epinephrine present in the perfusate. Snyder[7-10] attributed the increased hepatic outflow under the influence of epinephrine to the dilator action of the drug on the hepatic veins, or more probably to the fact that fluid was being suddenly added to the hepatic venous outflow as a result of the giving up of water by the parenchymatous cells of the liver. Schmid[11] showed that epinephrine produces the greatest decrease of the portal blood flow at the moment when it causes the highest rise of portal pressure. He explained the effect as being due mainly to the action of epinephrine on the vessels of the liver. Burton-Opitz[12, 13] showed that epinephrine produces constriction of the ramifications of the hepatic artery and of the portal vein within the liver. Macleod and Pearce[14] studied the effect of epinephrine on the outflow of blood from the liver and attributed the decrease of outflow to the constrictor effect of the drug on the portal ramifications within the liver.

Edmunds[15] obtained an increase of hepatic volume by administering epinephrine intravenously after ligation of the hepatic artery. He attributed the increase of hepatic volume to the damming back of blood in the inferior vena cava. Mautner and Pick[16] found that the effect of epinephrine, either on the intact animal or on the isolated liver, is to produce marked constriction of the hepatic capillaries. Bainbridge and Trevan[17] observed a rise of portal pressure and an increase of hepatic volume after administration of epinephrine. The increase of hepatic volume was attributed to obstruction of the flow of blood from the liver into the systemic circulation. They stated that the most probable cause of the obstruction is a narrowing of the hepatic sinusoids, which is produced by swelling of the hepatic cells. Lamson and Roca[18] stated that the liver is a unique organ whose circulation possesses a constrictor mechanism on the venous side of its capillaries, and that this constrictor mechanism in the dog is under nervous control and can be acted on by epinephrine, which brings about an obstruction of outflow of blood by narrowing the hepatic veins. Loeffler and Nordmann[19] transilluminated the mammalian liver in situ and observed marked paling of the regions under observation whenever epinephrine was applied locally or given intravenously. They attributed the paling to narrowing or complete closure of the capillaries and other vessels in the field of observation.

Lampe[20] suggested that epinephrine causes constriction of only portions of the vessels, possibly the precapillaries, in the perfused liver. Lampe and Mehes[21] observed that epinephrine causes a decrease of hepatic outflow and a diminution of hepatic volume. They attributed these changes to constriction of the vascular ramifications within the liver. Baer and Rössler[22, 23] observed a decrease of hepatic volume when epinephrine was added to the perfusate. They concluded that both the hepatic and the portal ramifications within the liver are endowed with a vasomotor mechanism which is stimulated by epinephrine. McLaughlin[24] noted that the perfused livers of dogs and cats consistently gave a decreased outflow under the influence of epinephrine. The epinephrine was thought to act on the intrahepatic portal radicles. Bodo and Marks[25] found that the addition of epinephrine to the perfused mammalian liver caused a considerable rise of arterial pressure when the epinephrine entered the liver through both the hepatic artery and the portal vein, but, when it was administered only through the portal route, the rise of arterial pressure was less marked than when it was administered by both routes. Clark[26] observed a rise of portal pressure in the intact cat and a considerable decrease of hepatic volume and perfusion flow under the influence of epinephrine. He explained the rise of portal pressure and the reduction of perfusion flow as due to the constrictor action of epinephrine on the intrahepatic vessels, and not to swelling of the hepatic cells. Mattson[27] observed a rapid and pronounced decrease of hepatic volume in every experiment in which epinephrine was administered intravenously.

Grab, Janssen, and Rein[28, 29] found that giving small doses of epinephrine intravenously caused the hepatic outflow to exceed the inflow to such an extent that about 59 per cent of the weight of the bloodless liver might be lost during the period of excess outflow. They suggested that epinephrine relaxes the efferent hepatic veins. Carnot, Gayet, and Merklen[30] consistently observed elevation of portal pressure after injection of epinephrine. The rise of pressure was attributed to the constrictor effect of epinephrine on the arterioles in the portal regions. Griffith and Emery[31, 32] attributed the decrease of hepatic volume to the asphyxial secretion of epinephrine which caused constriction of the intrahepatic vascular ramifications. They observed a decrease of hepatic volume when epinephrine was administered into the hepatic artery. By means of the Rein thermostromuhr, Schwiegk[33] observed an increase of flow in the hepatic artery when small doses of epinephrine were given in the form of continuous infusions, but the plethysmographic record of hepatic volume gave variable results—sometimes an increase, at other times a decrease. With the administration of epinephrine, Bauer, Dale, Poulsson, and Richards[34] observed constriction of the ramifications of both the hepatic artery and the portal vein. They stated that epinephrine opens the sluice mechanism located near the openings of the hepatic veins into the inferior vena cava. McMichael[35] observed a decrease of

hepatic volume when epinephrine was administered. He suggested that the constrictor effect of epinephrine must be on the portal venous ramifications in the liver, and not on the sublobular hepatic veins.

Rüegg[36] found that, in the perfused liver of the dog, epinephrine might cause either an increase of outflow by producing diminished portal resistance, or a decrease of outflow accompanied by a rise of portal resistance. Pak and Read[37] compared the effect of ephedrine with that of epinephrine on the hepatic circulation of dogs and cats. Ephedrine caused a prolonged rise of the portal pressure of dogs, but the rise was not as marked as that produced by epinephrine. The rise of portal pressure was attributed to vasoconstriction of the portal ramifications. Tschernogoroff and Popoff[38] perfused the liver of the dog in situ, and observed a decrease of hepatic volume and a rise of portal pressure on administration of epinephrine. With large doses of epinephrine, Katz and Rodbard[39] observed a rise of portal pressure and a sharp decrease of portal flow, followed sometimes by an increase, with a final return to the control level; but in small doses the portal flow may increase while the venous pressure falls. Chakravarti and Tripod[40] noted the following three actions of epinephrine on the perfused liver: (1) the sluice mechanism at the entrance of the hepatic veins into the inferior vena cava was opened, thus removing the resistance on the venous side and decreasing the volume of the liver; (2) the resistance on the inflow side was increased by constriction of the ramifications of both the hepatic artery and the portal vein in the liver; and (3) when the epinephrine already in the perfusate caused a decrease of hepatic volume, the added epinephrine caused an increased resistance on the outflow side. Sympathomimetic drugs—tyramine, ephedrine, veritol, sympatol, and benzedrine—acted like epinephrine except that their effects were much more prolonged.

Results.—A. Observations on the amphibian liver: One-tenth cubic centimeter of a 1:10,000 to 1:100,000 solution of epinephrine hydrochloride, when administered intravenously, or the direct application of a drop over the region under observation, repeatedly caused constriction of the sinusoids of the liver, regardless of whether they were arterial, portal, or hepatic venous. The time which elapsed between the administration of epinephrine and the constrictor effect on the sinusoids of the liver was brief; it varied between five and ten seconds. The duration of the constrictor effect was roughly proportional to the concentration of epinephrine administered. However, the arteriovenous anastomoses, as well as the points of origin or bifurcation of the vessels, were affected most conspicuously. When the lower dilutions were used, the arteriovenous anastomoses constricted to the point of disappearance, and most sinusoids in the region under observation contracted to such an extent that the individual corpuscles were squeezed tightly into single file in the lumen. When higher dilutions of epinephrine were administered, the arteriovenous anastomoses contracted slightly, but the force

of arterial flow was so strong that blood was pushed in both directions through the vein at the anastomoses and reversed the direction of flow distal to the arteriovenous anastomoses. The flow in both directions in the vein at the arteriovenous anastomoses lasted for more than two minutes, and the sinusoids draining into that vein became efferent sinusoids; that is, they carried blood away from that vein into the lobule which they traversed, instead of draining it into that vein as they did before the administration of epinephrine. After the constrictor effect of epinephrine wore off—which was usually within three minutes, except in the case of very low dilutions, in which it lasted a little longer—there followed a gradual reactivation of the whole lobule, with engorgement of the sinusoids by the packed corpuscles in the rapidly flowing stream through their lumina. At this stage the arteriovenous anastomoses were wide open, and the reverse flow increased to such an extent that it completely overcame the draining stream and made of the whole region a supplying, instead of a draining system.

Direct application of a drop of 1:10,000 solution of epinephrine hydrochloride caused, in addition to the constriction of the sinusoids and arteriovenous anastomoses, shrinkage of the hepatic lobule to such an extent that the region under observation pulled away from the objective of the microscope.

B. Observations on the mammalian liver: Solutions of 1:10,000 to 1:100,000 epinephrine hydrochloride, when administered in amounts of 0.1 c.c. into the portal vein or the inferior vena cava, or two drops applied directly through a fine needle over the illuminated region, repeatedly produced a constrictor effect on the sinusoids of the liver, regardless of whether they were arterial, portal, or hepatic venous, or whether they were located in the periphery or center of the lobule. The constrictor effect produced by direct application of epinephrine appeared within ten seconds and lasted two to four minutes, after which, reactivation of the sinusoids took place gradually. With the higher dilutions the reactivation of the constricted sinusoids was accompanied by activity of the sinusoids that were inactive in the field under observation prior to the application of the drug. When the more concentrated solutions were applied, the region became very much blanched with almost total disappearance of corpuscles from the extremely contracted sinusoids during maximal constriction; and, as the effect of the drug wore off, not all of the sinusoids became reactive. The duration and the degree of blanching varied roughly in proportion to the concentration of the solution of epinephrine which was applied.

Of the two intravenous routes of administration, that by way of the portal vein gave a much more lasting and a stronger constrictor effect than that by the caval route. The constrictor effect produced by the injection of epinephrine into the inferior vena cava lasted, invariably, less than four minutes, and rarely appeared before ten seconds after the injection. Injecting the same amount and dilution of epinephrine

into the portal vein caused, within five seconds, marked constriction of the sinusoids under observation, and more than four minutes elapsed before activity became as it was prior to the injection. When the contracting sinusoids trapped corpuscles in their lumina, the constrictor effect of epinephrine seemed more conspicuous at the point of entrance of the sinusoids into the draining veins, which was the only region where no lumen could be discerned during the effect of epinephrine. On several occasions erythrocytes were seen outside the lumen of the sinusoid, between it and the bordering hepatic cells. This seems to indicate the presence of regional deficiencies in the walls of sinusoids.

It was observed that when the drug was administered into the inferior vena cava the constrictor effect was replaced within four minutes by overactivity of the circulation in the whole liver, both as to number of active sinusoids and as to engorgement and rate of flow of blood in them. More than twenty minutes elapsed before the activity subsided to the preinjection state. The effect of epinephrine on the anastomoses between the ramifications of the portal vein and the hepatic artery in the periphery of the lobule was also studied. The ramifications of both the portal vein and the hepatic artery were narrowed considerably for more than one minute, and the communications between them disappeared until the constrictor effect wore off, after which each anastomosis looked much larger than it was prior to the injection of epinephrine.

ACETYLCHOLINE

Literature.—Snyder[7-10] showed that a vagus stuff is liberated into the perfusate of the isolated liver of the turtle as a result of stimulation of the vagus nerve. He also demonstrated that acetyl-β-methylcholine increases the rate of outflow from the liver when the pH is 7.0, and decreases it at a pH of 7.5. In another publication, he attributed the reduction of hepatic volume to the decrease in portal inflow caused by the vasoconstrictor effect of acetyl-β-methylcholine on the portal venous bed. He stated that the cholinergic drug, as well as the impulses of the motor vagal nerve, produces constriction of the hepatic venous sphincters. In his latest publication, Snyder[9] explained the effects of cholinergic drugs as being due to peristaltic constriction of the hepatic venules and the hepatic vein, without active participation of the hepatic sinusoids. Hunt[41] stated that acetylcholine has a dilator action on the terminations of the hepatic artery, and that this effect disappears when the artery is ligated. Bauer, Dale, Poulsson, and Richards[34] found that acetylcholine had hardly any perceptible effect on the ramifications of the hepatic artery or of the portal vein. McMichael[35] stated that, with large doses of acetylcholine, he obtained constriction of the portal branches and a rise of portal pressure. Katz and Rodbard[39] noted that acetylcholine in amounts up to 10 micrograms did not have any effect, but in doses of more than 100 micrograms it produced a fall of the portal and arterial pressures and a decrease of

portal flow. When Chakravarti and Tripod[40] injected acetylcholine into the portal vein, they did not observe any increase of hepatic volume, but when the drug was injected into the hepatic artery, the increase of hepatic volume was attributed to increased arterial flow and to diminution of outflow.

Results.—A. Observations on the amphibian liver: Solutions of 1:100,000 to 1:10,000,000 of acetylcholine bromide were applied directly to the region under observation or injected into the vein leading to the liver. Neither by direct application nor by intravenous administration were any observable effects produced on the circulation in the liver: the sinusoids did not show either constriction or dilatation. The arteriovenous anastomoses in fields under observation were also unaffected by the acetylcholine. However, at times, after the acetylcholine reached the heart, the liver became temporarily congested from stasis of the blood in the sinusoids produced by the transient "standstill" of the heart which was brought about by the parasympathomimetic drug.

B. Observations on the mammalian liver: Solutions of 1:10,000 to 1:10,000,000 of acetylcholine bromide were administered either by direct application to the region of the liver under observation or by injection into the portal vein. Neither by direct application nor by intravenous administration were any observable effects produced on the circulation of the intact liver: the sinusoids did not show either constriction or dilatation. In two experiments, there was one arteriovenous anastomosis in the interlobular margin. The acetylcholine did not have any effect on the anastomosis in either case. When the higher concentrations were administered, the drug slowed the heart, and, as a result, slowing of the flow in the sinusoids and some engorgement followed. In some experiments the heart stopped for about fifteen seconds, during which there were real engorgement of the liver and stasis in the sinusoids. However, the activity of the sinusoids returned to the preinjection state as soon as the heart began beating vigorously after the effect of the parasympathomimetic drug wore off. A few experiments were tried with very large doses of acetylcholine (0.3 c.c. of 1:1,000 solution), administered into the portal vein. An immediate but transient constriction of the portal branches was observed.

GLUCOSE

Literature.—Mautner[42] observed a long-lasting increase of hepatic volume after intravenous administration of glucose, levulose, and maltose. He suggested that the lysis water released during the formation of glycogen from these sugars is the probable cause for the increase of hepatic volume. Mattson[27] found that glucose or levulose, when given intravenously, produced definite increases of hepatic volume which were greater than those produced by the injection of equivalent amounts of physiologic saline solution. After the intravenous in-

jection of 20 c.c. of a 40 per cent solution of glucose, Schwiegk[33] found that the blood flow in the hepatic artery increased to double the control volume, whereas the portal flow increased 10 per cent. Lichtwitz[43] expressed the belief that there is a "functional coordination between the chemism of the liver and its circulation." Free hepatic circulation assures the delivery of dextrose to the consuming organs.

Results.—A. Observations on the amphibian liver: Slow intravenous injection of 1 c.c. of a 10 per cent solution of glucose per 25 Gm. of frog body weight produced an increase in the circulatory activity of the liver. This observation was confirmed repeatedly in different lobules of the liver of the same animal and in the livers of different animals. For example, in one region under observation, twenty-eight sinusoids were inactive, but contained motionless corpuscles in their lumina before injection. Six minutes after the slow injection of 1 c.c. of a 10 per cent solution of glucose, twenty-three sinusoids became active, and before the end of ten minutes no inactive sinusoids were seen in the field. This increase of activity continued for more than two hours. Sufficient observations have been made, and all showed that when glucose *is slowly administered intravenously it increases the circulatory* activity in the hepatic lobules. Under similar conditions, control experiments were performed by substituting the same quantity of frog Ringer's solution for the glucose. No noticeable increase of circulatory activity in the liver was manifested in the controls.

B. Observations on the mammalian liver: Slow intravenous administration of 1 c.c. of a 10 per cent solution of glucose in Ringer's solution per 50 Gm. of rat body weight led within three minutes to a gradual increase of circulatory activity in the liver. Before the lapse of fifteen minutes after the injection, practically all the hepatic lobules and their sinusoids were in full circulatory activity. The lobules or portions of lobules that were active prior to injection continued in full activity, and those that were inactive became active. Even the short transverse and oblique sinusoids which connect the radial ones became patent and fully active. This marked increase of circulatory activity lasted more than two and a half hours, after which a gradual return to the preinjection state was observed. Under identical conditions, *control experiments were performed by substituting Ringer's solution* without glucose. No perceptible change in the circulatory activity of the livers of the control animals could be observed.

THYROXIN

Results.—A. Observations on the amphibian liver: Daily injections of 1 mg. of thyroxin into the dorsal lymph sac for a period of ten to twenty days, or the feeding of thyroid for the same period produced a great increase of circulatory activity in the liver. To the naked eye the exposed livers appeared much redder than those of the controls. Microscopic examination of the transilluminated liver in situ showed

that practically all the lobules were in the active state, in contrast to the controls, in which the majority of the livers were comparatively inactive. There were many more patent arteriovenous anastomoses between corresponding branches of the portal vein and the hepatic artery, and of the hepatic artery and the hepatic vein, and also many more regions of sinusoids supplied with arterial blood in the livers of frogs to which thyroxin or thyroid had been administered than in the controls. Three per cent of the frogs died during the period of administration, and two per cent did not show any noticeable increase of circulatory activity in their livers. All the others manifested the described changes of their hepatic circulation, plus a loss of weight ranging from 2 to 8 grams.

B. Observations on the mammalian liver: Daily subcutaneous injections of 0.05 to 0.1 mg. of thyroxin per 50 Gm. of rat body weight over a period of ten days caused a marked increase of circulatory activity in the liver. From the second day, the liver began to look hyperemic, and, on microscopic examination, a slight increase of circulatory activity was observed. About the sixth day of administration of thyroxin, the increase of circulatory activity in the liver attained its maximum, during which there was complete activity of all sinusoids of the liver. The intermittence, or shift, of circulatory activity that was observed in the control livers was no longer present under the influence of thyroxin. There were scarcely any sinusoids or portions of lobules which could be considered in the resting phase. Even the oblique and transverse sinusoids were active, and the whole liver pulsated from the increased circulatory activity. Arteriovenous anastomoses in the interlobular spaces between the hepatic artery and the portal vein were observed more frequently in livers of rats which received thyroxin than in the controls.

After the administration of thyroxin was stopped, the circulatory activity in the liver took about two weeks to subside to the normal state and show the intermittence and alternation that were observed in the hepatic circulation of the control rats from the same litter.

PARTICULATE MATTER AND DYES

Results.—A. Observations on the amphibian liver. India ink: Injection of 0.2 c.c. of a 1 per cent suspension of India ink into the lymph sac, within a period of five to twelve minutes, led to a gradual increase of circulatory activity in the hepatic lobules. Within forty-five minutes there remained practically no region of the liver in which the circulation was not active. Almost every sinusoid was patent, and blood was rapidly coursing through it, with many particles of ink carried in the stream. Many arteriovenous anastomoses became patent. At the same time the reticulo-endothelial cells of Kupffer gradually became loaded with particles of ink. After about two hours from the time of injection, the Kupffer cells became so loaded with black particles

that the whole liver became extremely dark. At this stage the circulation of the liver became much less active than before, and many sinusoids were observed in various phases of inactivity. The Kupffer cells were seen in the walls of the sinusoids, and were located most commonly at the bends. Often Kupffer cells loaded with particles of India ink were seen projecting into the lumen of a sinusoid, but they were never seen in the lumen of a sinusoid with strands connecting them to the wall.

Dyes: The intravenous administration of 0.05 c.c., or the injection into the lymph sac of 0.2 c.c. of a 1 per cent solution of methylene blue, or of gentian violet, led in a few minutes to a marked increase of the circulatory activity in the liver which continued for more than three hours. The regions in which sinusoids had been in various stages of inactivity before the dye was injected became so active that practically every sinusoid was opened, with blood rapidly coursing through it. Under the influence of the dye no increase in the number of patent arteriovenous anastomoses in the regions under observation was noticed.

B. Observations on the mammalian liver. India ink: Injection of 0.1 to 0.2 c.c. of a 10 per cent suspension of India ink in mammalian Ringer's solution into the inferior vena cava led, within two minutes, to a gradual increase of circulatory activity in the liver. Within ten minutes practically every lobule in the liver was active, and the sinusoids were filled with blood and particles of ink which rapidly streamed through them. Thereafter, the *reticulo-endothelial* cells of Kupffer became evident by the presence of particles of ink within them. Observations were made for periods extending over six hours. No matter how dark the liver became, or how loaded the Kupffer cells were with particles of ink, the circulation remained active. It was repeatedly observed that the regions where the supply to the sinusoids was mainly arterial had the least number of Kupffer cells, and these were comparatively very slightly charged with particles of ink. Four or five sinusoids fed by ramifications of the hepatic artery could be traced all along their course toward the central vein, and no charged Kupffer cells could be detected in their lumina or in their walls, whereas, in the walls of the sinusoids supplied by the comparatively slower stream from the portal vein, many Kupffer cells could be observed and were loaded with particles of ink. Some of these charged Kupffer cells bulged into the lumen, and others were within the lumen, and connected to the wall by strands over and under which erythrocytes passed through the sinusoids.

SUMMARY

The effects of glucose, dyes, particulate matter, thyroxin, epinephrine, and acetylcholine on the intrahepatic circulation of blood in intact animals were studied in vivo by means of the quartz-rod transillumination technique. Glucose increased the intrahepatic circulatory activity. Particulate matter, India ink, and dyes increased the intrahepatic circu-

latory activity and stimulated the phagocytic action of the Kupffer cells. The Kupffer cells became loaded with particles shortly after the injection of India ink. In the frog no Kupffer cells were seen within the lumina of the sinusoids, whereas in the rat such cells were found within the lumina of the sinusoids and were connected by strands to the sinusoidal wall. Thyroxin caused an increase of the vascular activity within the liver to such an extent that one could rarely find any sinusoids in the inactive phase. Epinephrine produced blanching of the liver by causing constriction of the intrahepatic vascular ramifications, but acetylcholine did not have any preceptible vasodilator effect.

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AURICULOVENTRICULAR BLOCK WITH VENTRICULOAURICULAR RESPONSE

Report of Six Cases and Critical Review of the Literature

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Experiments on animals have shown that retrograde conduction is a normal function of the muscular conduction system.[1] Clinical experience, however, is not quite in accord with the experimental results, as this report will illustrate.

When A-V nodal rhythm is established by the action of a lower rhythm center which forms impulses at a more rapid rate than the sinoauricular pacemaker, block of the V-A (retrograde) conduction, giving rise to a complete or incomplete A-V dissociation,* is observed far more frequently than retrograde conduction, giving rise to a true A-V nodal rhythm of the whole heart. Retrograde conduction of the impulse in the case of ventricular extrasystoles occurs even less frequently, and retrograde conduction in which idioventricular rhythm arises below the bifurcation of the common bundle rarely occurs.

It is therefore surprising that retrograde response should occur, and show a normal or almost normal transmission time, when orthograde conduction is grossly impaired. We have been able to find nineteen such cases in the literature. Three further cases of our own are presented, together with three additional cases which were kindly put at our disposal by Dr. Louis N. Katz and Dr. John Parkinson.

CASE REPORTS

Case 1.—A woman, 62 years of age, with long-standing hypertension. An attack of dizziness without loss of consciousness, in July, 1937, was followed by a bradycardia of 35 beats per minute and a fall of the systolic pressure from 210 to 140. No drugs had been given prior to the attack, and there had been no complaints of anginal pain. The condition remained stationary for the whole time of our observation (over two months).

Electrocardiograms (six records on four nonconsecutive days within seven weeks).—

A. Sept. 11, 1937 (Fig. 1, *A*). There is complete A-V block, with idioventricular rhythm; the latter probably arises below the bifurcation of the bundle of His, at a regular rate of 37. There is "low voltage"; the QRS duration is 0.13 second. The sinus rhythm is

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Received for publication March 16, 1943.

*The term A-V dissociation is used in contradistinction to A-V block to indicate independent action of auricle and ventricle, not the result of impaired A-V conduction but resulting from the normal refractory period of the junctional tissue when the rate of the subsidiary pacemaker exceeds that of the sinus impulses transmitted to the subsidiary pacemaker.

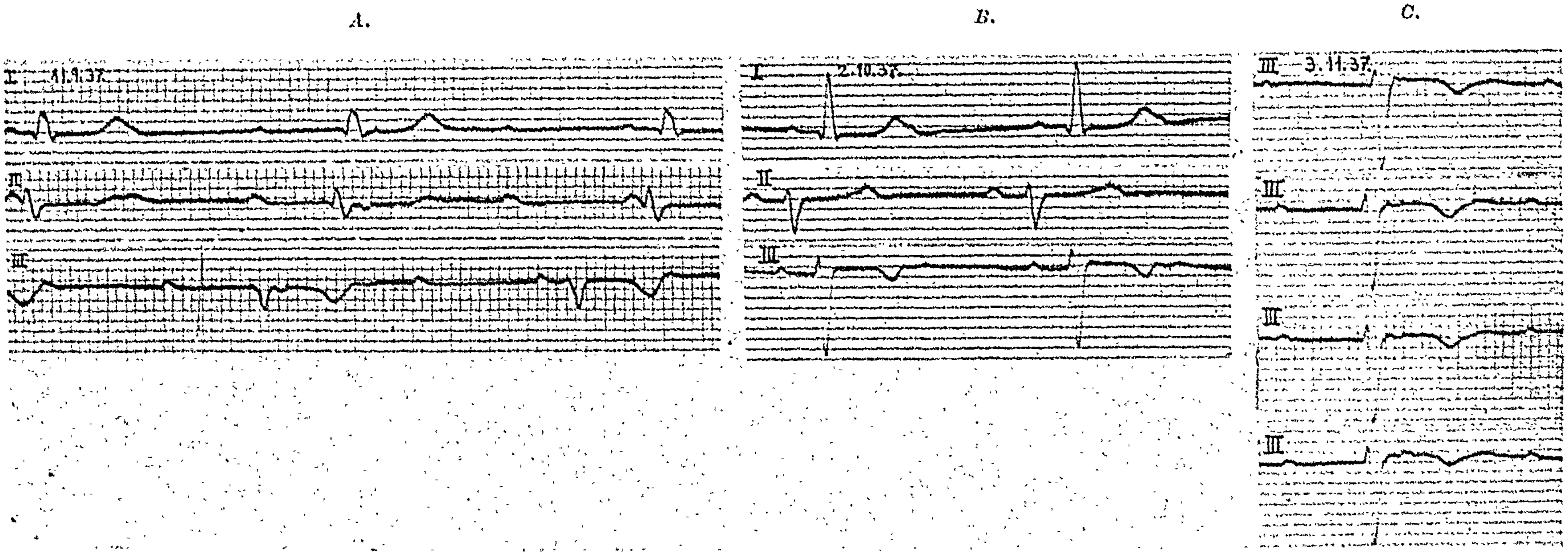

Fig. 1.—Case 1.

A, Complete A-V block with preserved V-A conduction. The fourth auricular deflection in Leads I and II and the third P in Lead III are retrograde responses. The retrograde P is upright in Lead I and inverted in Leads II and III.

B, Three weeks after *A*; 2:1 response. No retrograde P waves.

C, Four weeks after *B*; four idioventricular beats of supraventricular origin. The occurrence of retrograde P waves depends upon the length of the preceding P-R. Only the two middle tracings show retrograde conduction as evidenced by premature and inverted P waves after the QRS. In the upper tracing, retrograde conduction fails because P-R is too long and the normal orthograde P supervenes, whereas, in the lower tracing, retrograde conduction fails because P-R is too short and the retrograde impulse is blocked.

Time intervals = 0.05 second; 1 millivolt = 1 cm.

slightly irregular because of the varying position of P in relation to the ventricular complex; the P-P intervals which include a ventricular beat are shorter than the P-P intervals which do not.

The fourth auricular beat (P′) in Leads I and II and the third in Lead III are definitely premature. Each follows R by an interval of 0.15 second, is upright and small in Lead I, and inverted in Leads II and III. The following interauricular interval (P′-P) is lengthened and compensates for the shortening of the preceding P-P′. Whenever P-R is within the limits of 0.415 to 0.450 second, a similar arrhythmia occurs. When P-R is under 0.410 second, or above 0.550 second, the subsequent P is normal in shape and occurs at the expected time. Within the range for P-R of 0.460 to 0.550 second, P′ occurs within the limits of normal P-P intervals or is slightly premature. It differs from the other P′'s in not being inverted in Leads II and III, and also differs from the normal P in minor details; however, its shape is difficult to recognize because of the superposition on T.

As shown, the premature auricular beats represent ventriculoauricular responses. The intermediate character of responses in late auricular diastole is produced by the fusion within the auricles of the normal sinoauricular impulse with the retrograde impulse. Such beats, resulting from simultaneous stimulation of the same portion of the heart by two impulses, might be termed "fusion beats,"[2] in contradistinction to beats showing "superposition" in the electrocardiogram, i.e., algebraic summation of electrograms of various portions of the heart stimulated simultaneously.

B and C. Sept. 18, and Oct. 2, 1937 (Fig. 1, *B*). There is 2:1 auriculoventricular response throughout, and sinus arrhythmia with alternation of the P-P intervals; those which contain a ventricular complex are shortened. This is common in A-V heart block, and we propose to call it "ventriculophasic sinus arrhythmia in heart block."

D. Nov. 3, 1937 (Fig. 1, *C*). There is a high-grade, incomplete A-V block; the ventricles are controlled for the most part by an idioventricular pacemaker, and orthograde impulses are transmitted only in late ventricular diastole. When R-P exceeds 1.58 seconds, the R-R of the idioventricular rhythm measures 1.92 seconds, and conduction takes place with a P-R of 0.22 to 0.26 second. Idioventricular and conducted ventricular complexes differ only in minute details, and are

TABLE I

REFRACTORY PERIOD FOR ORTHOGRADE (A-V) AND RETROGRADE (V-A) CONDUCTION IN CASE 1

DATE	RHYTHM	ORTHOGRADE CONDUCTION			RETROGRADE CONDUCTION		
		P-R	LONGEST R-P NOT FOLLOWED BY CONDUCTION	SHORTEST R-P FOLLOWED BY CONDUCTION	R-P′	LONGEST P-R NOT FOLLOWED BY CONDUCTION	SHORTEST P-R FOLLOWED BY CONDUCTION
9/11/37	Complete A-V block, idioventricular rhythm	∞	1.37		0.15	0.41	0.415
9/18/37	2:1 A-V block	0.205	0.54	1.25			
10/ 2/37	2:1 A-V block	0.205	0.53	1.28			
11/ 3/37	Incomplete A-V block with interference-dissociation	0.22–0.26	1.58	1.53	0.15	0.45	0.47

almost identical with the ventricular complexes at the time of 2:1 response (Fig. 1, *B*). Ventriculophasic sinus arrhythmia is present. Ventriculoauricular responses are of rare occurrence, and are spotted most easily when the longest P-R intervals are examined closely. Although P-P′ does not exceed the lower limits of normal interauricular periods (P-P) as measured in the whole curve, it is shorter than the average P-P. P′ is inverted in the two middle tracings, but not in the upper and lower.

Table I gives a summary of our observations in this case.

CASE 2.—A man, 76 years old, showed signs of congestive heart failure in February, 1937, with slight anginal pain on effort. There were never any fainting spells. Prostatectomy without complications was done at the age of 70 years; glycosuria had been found at the age of 69 years. When first seen by one of us (M. W.) on Aug. 25, 1937, his blood pressure was 220/80, and his pulse rate, 48. There were left ventricular enlargement, severe congestive failure, and a periodic type of breathing without distinct periods of apnea. Digalen was administered daily, in a dose corresponding to 0.2 Gm. of the powdered leaves, from August 29 until August 31, and in a dose corresponding to 0.15 Gm., from September 1 until September 10. Two injections of a mercurial diuretic (novurit) were also given. The edema subsided considerably, and the general condition improved markedly up to September 11, when he developed frequent "attacks," with loss of consciousness; once he injured himself by falling, but had no convulsions. When digalen was discontinued, his attacks stopped immediately, but the patient was in a state of confusion for several days and complained of severe headache on subsequent days. Nothing of note was observed later; the patient's compensation was maintained by means of 0.05 to 0.1 Gm. of powdered digitalis leaf daily, and occasional intravenous administrations of novurit. He died from cerebral hemorrhage in July, 1938. Permission for a post-mortem examination was not obtained.

Electrocardiograms (seventeen records on twelve nonconsecutive days within six months).—

A. Aug. 25, 1937. The record shows complete A-V block with idioventricular rhythm. The auricular rate is 66, without marked arrhythmia. The ventricular action is regular at a rate of 47 to 50 per minute. QRS measures 0.12 second. The auricular rhythm, which is controlled by the sinus node, is disturbed at times by premature auricular complexes (P′) similar to those in Case 1. These premature P waves in Lead I differ from the normal P wave, in that they are slightly notched, and are inverted in Leads II and III. The premature P waves follow an idioventricular beat at an interval of 0.13 to 0.15 second and occur only at a P-P′ distance of 0.77 second or more (after a P-R of 0.62 second or more), while the normal P-P interval is about 0.91 second. The subsequent P′-P is lengthened without, however, fully compensating for the preceding shortening. Considering the abnormal P′ as retrograde P waves, the noncompensatory pause indicates that the retrograde impulse reaches the sinus node and disturbs its rhythmic impulse formation.

B. A record taken three days later shows essentially the same features.

C. Aug. 31, 1937 (Fig. 2, *A*, *B*, and *C*), third day of digitalis treatment. Here we have complete A-V block, with a few retrograde beats at P-P′ intervals of 0.75 second and more. R-P′ varies from 0.11 to

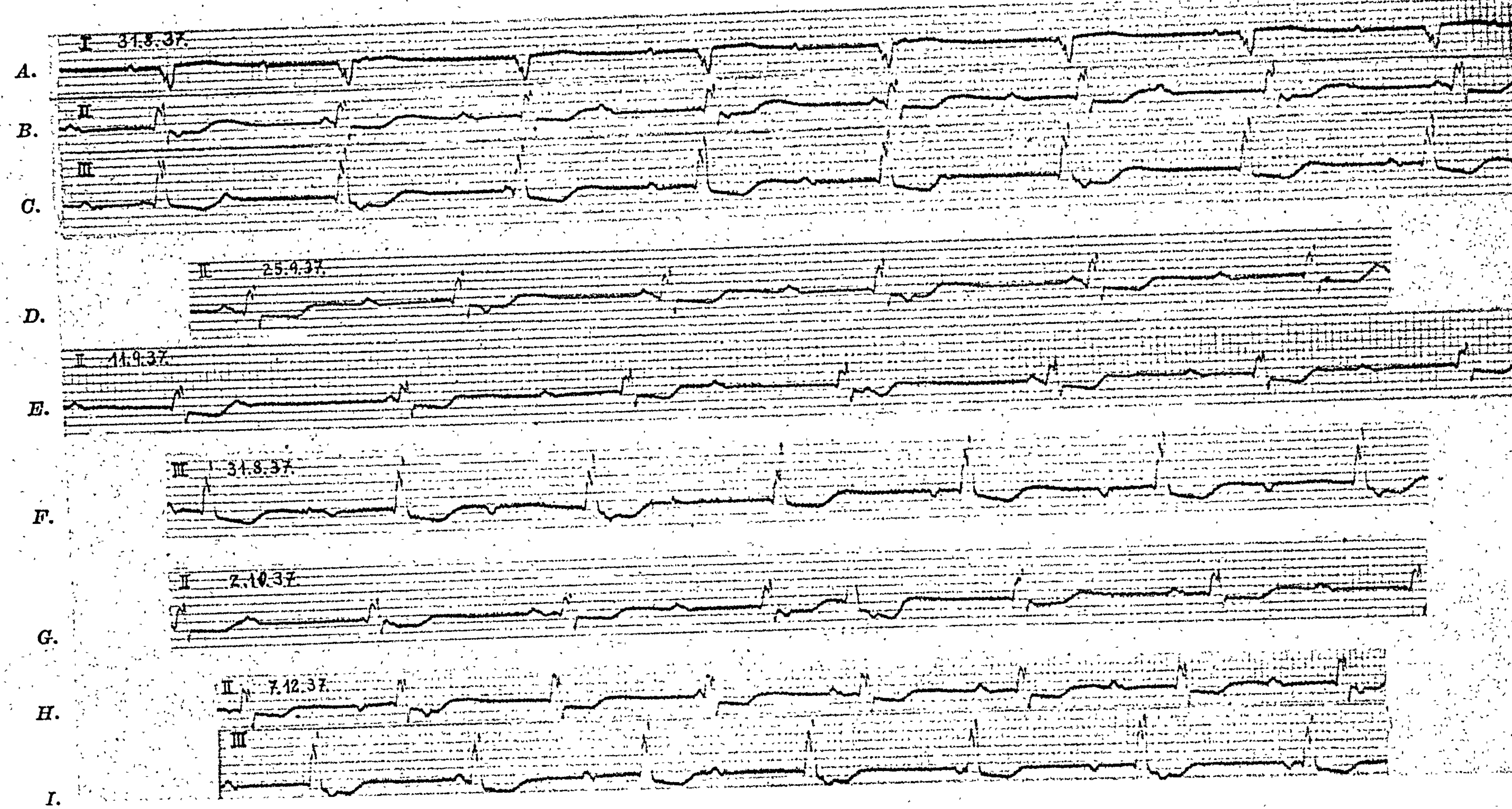

Fig. 2.—Case 2. Complete A-V block.

A to *C*, Retrograde conduction evidenced by the third and seventh P in Lead I, the second, sixth, and tenth P in Lead II, and the third and eighth P in Lead III. Note the upright P of retrograde conduction in Lead I.

D, Effect of digitalis. Retrograde conduction time (R-P′), previously 0.11-0.17 second, now measures 0.18 to 0.22 second. The absolute refractory period for retrograde conduction is also longer than before digitalization. Its duration is indicated by the second idioventricular beat with a P-R of 0.60 second, followed by retrograde conduction, and the sixth idioventricular beat with a P-R of 0.57 second, followed by retrograde block.

E, On the verge of digitalis poisoning. Complete retrograde block; otherwise, the first and last QRS should be followed by a retrograde P because of their long P-R distance.

F, Carotid sinus pressure produces slowing of the auricles, with inverted P waves throughout; these most likely represent the escape of an A-V nodal rhythm with orthograde block. The third and last QRS are followed by a premature P because of retrograde conduction of the idioventricular impulse.

G, An idioventricular beat with retrograde conduction is followed by a ventricular premature systole with retrograde conduction. The two retrograde P waves (P′) in succession occur at an interauricular period (P′-P′) which is shorter than the shortest period (P-P′) between a retrograde P and a preceding normal sinus P. The retrograde conduction time (R-P′) of the ventricular extrasystole is longer than the preceding R-P′.

H and *I*, Sinus arrhythmia with shifting of the pacemaker to the A-V node is responsible for the variations of P-wave contour. Retrograde conduction after inverted P waves occurs after shorter P-R distances than retrograde conduction after upright P waves; compare the second QRS in *H* and the sixth in *I* (both with short P-R followed by retrograde conduction) with the seventh in *H* and the third in *I* (both with long P-R followed by retrograde block). For explanation see text and diagram of Fig. 6.

Time intervals = 0.05 second.

0.17 second, in inverse proportion to the length of the preceding P-R. Fusion of an orthograde and late retrograde P is probable from the time relations, but is not reflected in the shape of the resulting P wave. Independent of retrograde conduction, there is a marked auricular arrhythmia with wandering of the pacemaker. The P waves are sometimes inverted, and show the same contour as the retrograde P waves (P′), but the time of their occurrence proves their independent origin. They are most likely retrograde responses to escapes of the A-V node which are blocked in the orthograde direction. These escapes occur mostly with a slowing of the auricles, such as follows retrograde conduction or is produced by carotid sinus pressure.

D. Sept. 11, 1937 (Fig. 2, *E*), at the time of digitalis intoxication. Here there are complete A-V and complete V-A block. The whole record, containing seventy-four ventricular cycles with every possible position of P, fails to show any sign of retrograde conductivity. The auricular action is very irregular, and multiple auricular escapes and extrasystoles are present. The idioventricular rhythm has also become irregular, and its rate ranges from 22 to 53. The disturbance of the idioventricular rhythm may explain the Adams-Stokes attacks which occurred on this day. Digitalis is also responsible for the alterations in the form of the ventricular complex.

E. Sept. 21, 1937, ten days after digitalis was discontinued. There is regular sinus action, with a rate of 63. There is no retrograde conduction. Several ventricular extrasystoles are present, interrupting the idioventricular rhythm.

F. Sept. 25, 1937 (Fig. 2, *D*). Here retrograde conduction has reappeared. It occurs only at a P-P′ of 0.82 second or more, and the transmission time (R-P′) is lengthened to 0.18 to 0.22 second. Thus. the absolute, as well as the relative, refractory period of retrograde conduction is affected by the accumulation of digitalis. Ventricular extrasystoles sometimes occur by chance after a retrograde P′. thus suggesting a "sandwiching," i.e., conduction from the ventricles to the auricles and back again to the ventricles. It can be easily shown, however, that such reciprocal rhythm does not occur in our case.

G. Oct. 2, 1937. Retrograde conduction occurs and the effect on it of digitalis administration has disappeared. In addition, there are numerous auricular extrasystoles with aberrant, upright P waves, auricular escapes with inverted P waves, and ventricular extrasystoles, some of them with retrograde conduction. This record and similar ones taken on other days made it possible to ascertain and compare the conditions for retrograde conduction after different types of auricular beats. It was found that retrograde conduction following inverted P waves occurred after shorter P′-R intervals than retrograde conduction following upright P waves, whatever the origin of the inverted P wave. The retrograde conduction time (R-P′) also tended to be shorter after retrograde auricular excitations.

Table II gives the data on one of several records taken on different days.

No significant features were added by later records. It was seen that, whenever an inverted P was due to supraventricular escape, it was followed by an idioventricular beat with retrograde conduction (Fig. 2, *H* and *I*), and, whenever two ventricular beats with retrograde conduction occurred in succession (Fig. 2, *G*), the second P′ of the pair occurred unusually early.

Thirty-five hundredths milligrams of strophanthin K, injected intravenously, failed to affect the rhythm. Barium chloride in doses of

TABLE II

REFRACTORY PERIOD FOR RETROGRADE CONDUCTION AFTER +P (SINUS P AND AURICULAR EXTRASYSTOLE) AND –P (RETROGRADE P AND ESCAPE) IN CASE 2*

		NO RETROGRADE CONDUCTION	RETROGRADE CONDUCTION WITH R-P′ 0.205-0.16	RETROGRADE CONDUCTION WITH R-P′ 0.15-0.135
P-R in 1/100 sec.	after +P	29, 30, 36, 58	56.5, 58, 88, 88	
	after –P	18, 19, 22, 28	28, 28, 33, 33.5, 36, 40 42, 42, 42.5, 43, 43.5, 48, 48	51.5, 54, 54.5, 56, 58

*For discussion see text.

TABLE III

VARIATIONS IN RETROGRADE CONDUCTION IN CASE 2

NUMBER OF RECORD	DATE	RATE		LONGEST P-R NOT FOLLOWED BY RETROGRADE CONDUCTION PLUS SHORTEST R-P′ (1)	SHORTEST P-P′	R-P′	NOTE
		AUR.	VENT.				
1	8/25/37	66	48	0.63	0.77	0.13-0.15	(1) To show upper limit of
2, 3	8/28/37	55	41	0.54	0.64	0.13-0.17	blocked retrograde conduction
4	8/31/37(2)	62	48	0.67	0.75	0.11-0.17	
5, 6	9/11/37(2)	54	22-53 (2)	>0.83			
7	9/21/37	63	41-45	>0.98			(2) Digitalis from 8/29/37 to 9/10/37
8-10	9/25/37	59	41	0.75	0.82	0.18-0.22	
11	10/ 2/37	60	33-44 (3)	0.71	0.73	0.13-0.16	
12	10/26/37	58	43	0.72	0.75	0.15-0.17	(3) Ventricular extrasystoles
13	11/ 2/37	50-92 (4)	41-48	0.67	0.71	0.14-0.16	
14	12/ 7/37	58	45	0.61	0.72	0.11-0.18	
15, 16	2/ 7/38	57	40	0.60	0.70	0.15-0.20	(4) Auricular extrasystoles
17	2/25/38	58	46	0.67	0.87	0.14-0.19	

0.03 to 0.09 Gm. daily, during three weeks, increased the auricular and ventricular arrhythmia, but was without effect on conduction or on the symptoms.

Table III shows the variations of retrograde conduction over the whole period of observation.

CASE 3.†—The patient was a man, 48 years of age. Bradycardia had been observed since 1936. At this time he complained of mild attacks of anginal pain. The blood pressure was 150/80; the blood Wassermann reaction was negative. Roentgenologic examination showed marked sclerosis of the aorta. Adams-Stokes attacks developed, and became more frequent as time went on. The patient succumbed to one of these attacks in August, 1938.

Electrocardiograms (four records of Lead II only, taken on four nonconsecutive days within seven weeks).—

A. Nov. 6, 1937 (Fig. 3, *A*). Complete A-V block alternates with 1:1 A-V response, probably partly because of the slight change in auricular rate. The sinus rate varies from 40 to 54 per minute as a result of

†We are indebted to Dr. Leo Hahn, Birmingham, England, formerly of Teplitz-Schoenau, Bohemia, for permission to use this case.

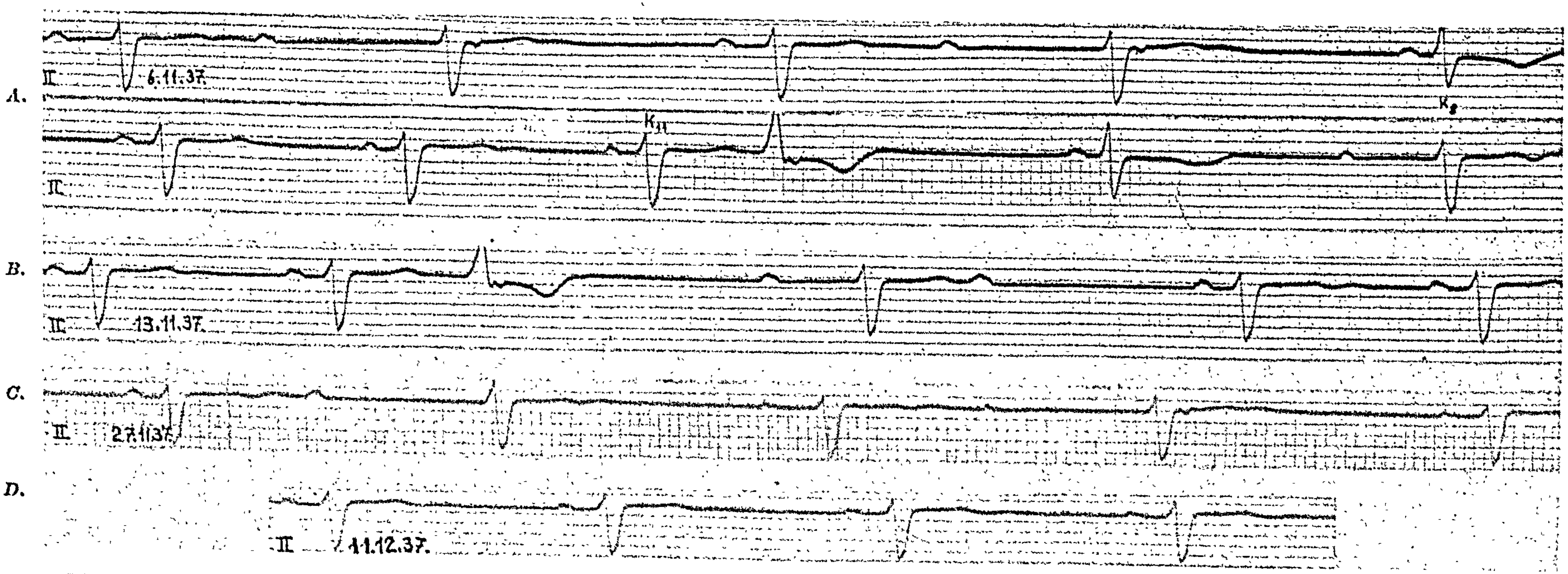

Fig. 3.—Case 3. (Courtesy of Dr. L. Hahn.)
Incomplete and unstable A-V block with retrograde conduction after both idioventricular beats and ventricular extrasystoles. The retrograde conduction time is shorter than the orthograde conduction time. For full discussion see text.
Time intervals = 0.05 second.

ventriculophasic sinus arrhythmia. The ventricular action is regular at 32 per minute, and QRS measures 0.14 second. Idioventricular and conducted beats do not differ in contour. The P-R interval, when conduction occurs, varies from 0.17 to 0.185 second. The second and fourth idioventricular beats (typical of others not shown) show retrograde conduction, producing an inverted P′, 0.15 second from the preceding R. This occurred whenever P preceded an idioventricular beat by 0.51 to 0.80 second. The P′ of retrograde conduction is not always premature, but it is invariably followed by a lengthened P′-P interval. The only ventricular extrasystole seen on this day (second strip) is followed by retrograde conduction, with a R-P′ interval of 0.15 second. The fifth ventricular complex (top line) and the first postextrasystolic complex show some difference in the shape of QRS and T. The time of their occurrence makes it likely that they result from fusion of idioventricular and conducted impulses. However, it is unlikely that fusion of impulses, both of which produce the same type of QRST, should result in an aberrant type unless improved conduction occurred after an exceptionally long ventricular pause and resulted in the ventricular complex aberration.

B. Nov. 13, 1937 (Fig. 3, *B*). Here we have 1:1 A-V response, interrupted on five occasions by ventricular extrasystoles. Each of these is followed by the premature P waves which represent retrograde conduction. The subsequent sinus P is blocked, and the ventricle escapes for one or two beats, until an auricular impulse occurs at a suitable interval after the end of the refractory period, when it is transmitted to the ventricle and 1:1 A-V conduction is resumed. The orthograde conduction time measures 0.18 to 0.20 second; and the retrograde conduction time, 0.15 second. The refractory period for orthograde conduction, with the exception of postextrasystolic block, ends at 0.57 to 0.62 second after idioventricular beats; retrograde conduction is confined to P-P′ intervals of 0.63 to 1.06 seconds.

C. Nov. 27, 1937 (Fig. 3, *C*). There is complete A-V block with ventricular complexes of the same type as before. The auricles are under the control of three foci: the sinoauricular node, the ventricular pacemaker (retrograde conduction), and a slow ectopic auricular focus with upright P waves. The retrograde conduction time measures 0.160 to 0.175 second, dependent upon the preceding P-R, and the pause after retrograde P waves is fully compensatory.

D. Dec. 11, 1937 (Fig. 3, *D*). There is normal A-V succession, and the auricles are stimulated by the ectopic center that was present on November 27. The auricular rate is 36 to 39, and P-R is 0.195 second.

SUMMARY OF OBSERVATIONS IN CASES REPORTED

Our three cases, as well as the nineteen cases found in the literature (all listed in Table IV) and the three additional cases (illustrated in Figs. 4 and 5, clinical data in Table IV), present certain identical features.

1. Inverted P waves occur at short intervals after idioventricular beats in cases of A-V block. These P waves, which we consider to be due to backward conduction of ventricular impulses to the auricles, are always inverted in Leads II and III; in Lead I, however, P′, as a rule, is either upright, diphasic, or isoelectric. It is upright in CF_2 and inverted in Lead IVR in the few cases in which these leads were recorded.

That the P′ of retrograde conduction is not the mirror image of the orthograde P was true also in nodal extrasystoles, in A-V nodal escapes, and in paroxysmal tachycardia of A-V nodal origin. This peculiar pattern of the retrograde P wave was found in the illustrations of such arrhythmias in various textbooks and monographs, as well as in ten out of twelve of our own recent cases. Attention has been drawn to it by Daniélopolu and Danulesco[3] and Wenckebach and Winterberg.[4]

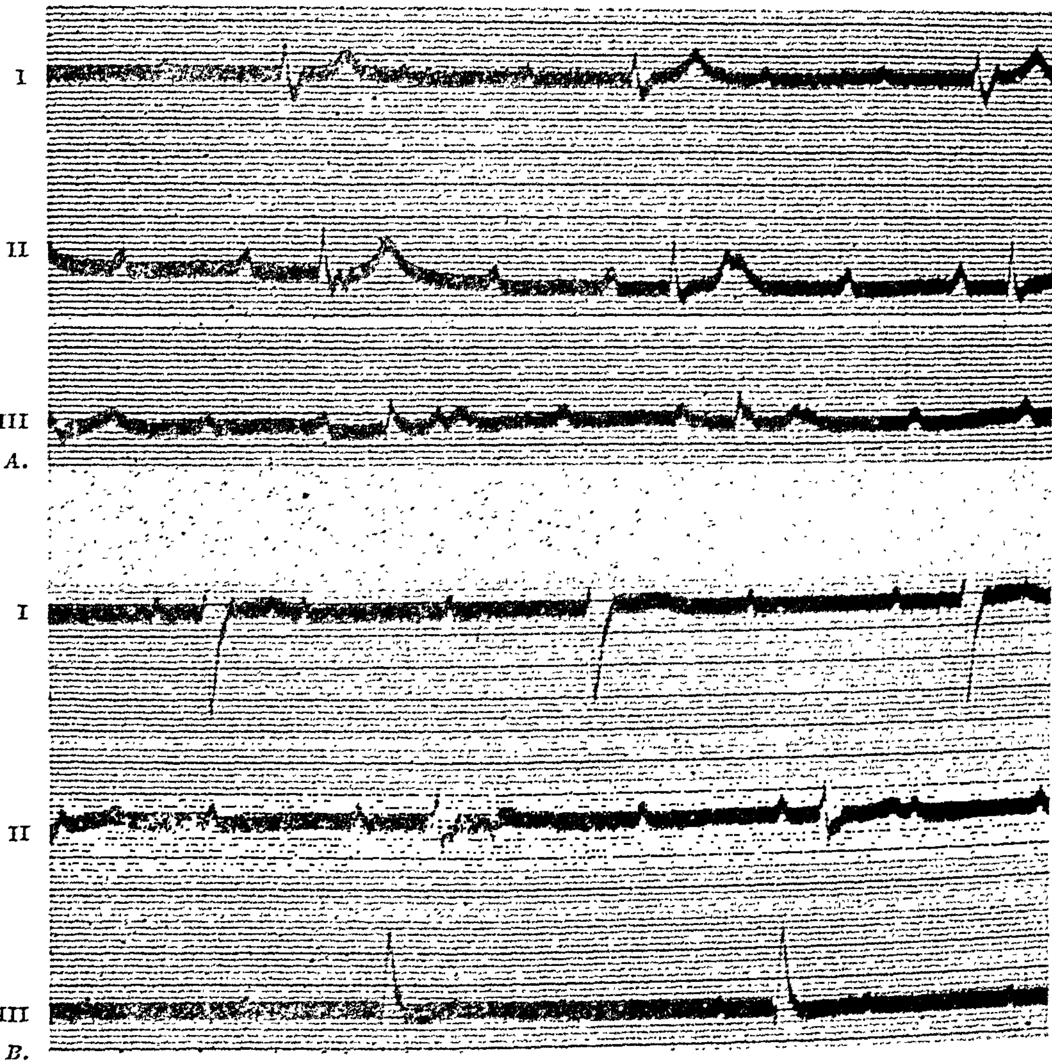

Fig. 4 (Courtesy of Dr. J. Parkinson).—Two cases of complete A-V block with retrograde responses of the auricles.

(*A*) The third P in Lead II, the first P in Lead III, and (*B*) the seventh P in Lead I (?), and the fourth P in Lead II are due to retrograde conduction. Note the marked prolongation of the retrograde conduction time (0.38 second) in case (*B*). The auricular pause after the retrograde P waves is fully compensatory, indicating that the retrograde impulse does not reach the S-A node.

Time intervals = 0.01 second.

2. In the majority of the cases the A-V block is of arteriosclerotic origin, and organic disease of the bundle of His is apparently the underlying condition. In only one case out of twenty (Table IV) was the patient under 48 years of age, and this case does not strictly belong in

the group because it is one of reciprocal rhythm. No case was encountered of congenital heart block, of A-V block due to myocarditis, or of A-V block following digitalis medication.

3. Unstable or incomplete A-V block, instead of complete block, occurred in more than half of our cases (Table IV). This seems to exceed the incidence of incomplete block in clinical heart block as a whole. It should be realized that the absence of conducted beats in a record does not necessarily prove that the conducting system is completely unable to transmit impulses. Partial A-V block with a long refractory period of the junctional tissue and a relatively rapid, passive, nodal or idioventricular rhythm can easily imitate complete A-V block. Theoretically, we are unable to rule out the possibility in any case of so-called complete A-V heart block that only partial A-V block exists, with complete A-V dissociation due to escape of the lower rhythm center.

I

II

III

CF₂

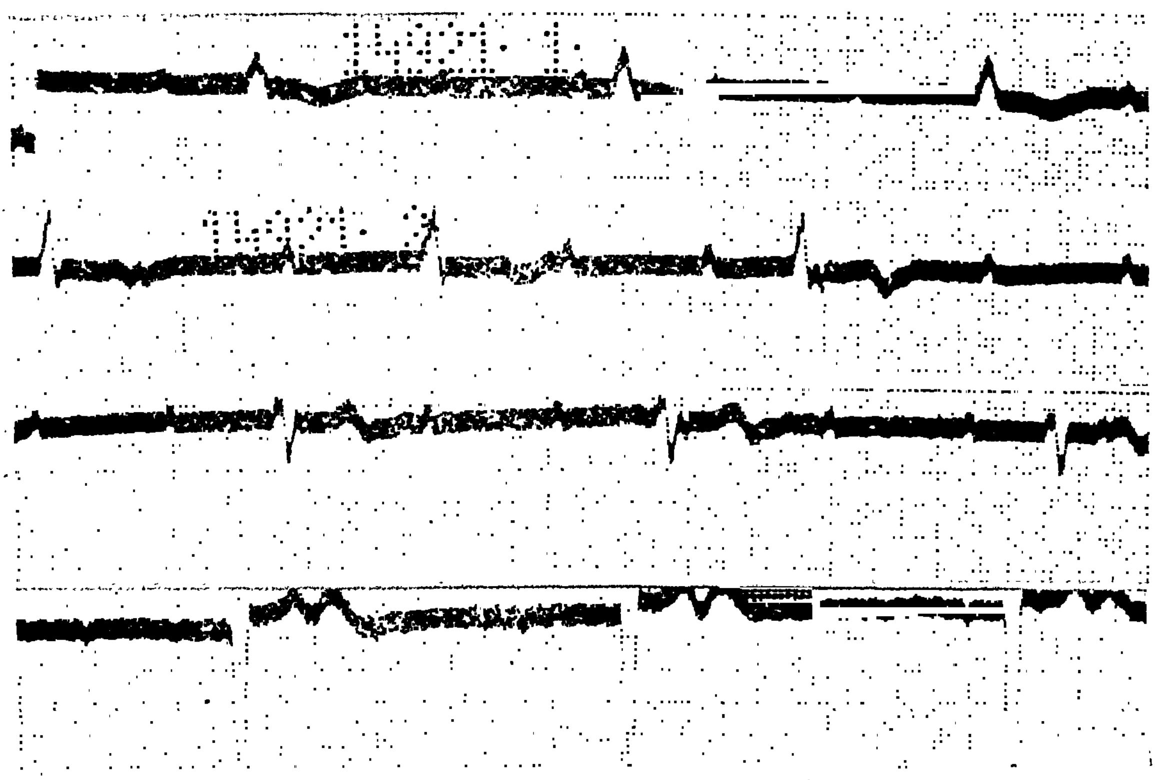

Fig. 5 (Courtesy of Dr. L. N. Katz).—Complete A–V block with retrograde response.

The third P in Lead I, the sixth P in Leads II and III, and the fifth P in Lead CF_2 represent retrograde P waves. The third P in Lead III, which is intermediate in contour between the sinus P and the retrograde P, is a fusion beat; it is only slightly premature, and is due to simultaneous invasion of the auricles by the orthograde impulse from above and by the retrograde impulse from below. Note the "ventriculophasic sinus arrhythmia of heart block": a P–P interval which contains a ventricular complex is shorter than a P–P interval which does not.

Time intervals = 0.04 second.

4. When incomplete block was present, retrograde conduction was confined to idioventricular impulses; the only exception was in a somewhat different case (Case 2 of Wolferth and McMillan[5]), in which reciprocal beats occurred in an instance of 2:1 A-V block.

5. Idioventricular rhythm arising below the bifurcation of the common bundle was present in all but five cases. However, it is possible that, in

TABLE IV

THE MAIN OBSERVATIONS IN ALL PUBLISHED CASES OF AURICULOVENTRICULAR BLOCK WITH VENTRICULOAURICULAR RESPONSE

NUMBER	AUTHOR	YEAR OF PUBLICATION	AGE	SEX	B.P. (SYSTOLIC)	WASSERMANN REACTION	VENTRICULAR RATE	AURICULAR RATE	ORIGIN (TYPE) OF IDIOVENTRICULAR RHYTHM	STABILITY OF BLOCK	DEGREE OF BLOCK	ORTHOGRADE P-R	RETROGRADE R-P'*	DIRECTION OF P_1'*	SHORTEST P-P'*	COMPENSATORY PAUSE	AURICULAR FUSION BEATS
1	Cohn and Fraser[7]	1913	62	M		? +	43	75	idiov.	unstable	2:1 and complete	0.20	0.10-0.14	?	0.64	+ ?	−
2	Wilson and Robinson, II[8]	1918		M		−	36-40	75-103	idiov., variable	stable	complete		0.20-0.34	?	0.58		
3	Daniélopolu and Danulesco[3]	1919	57	M		+	25	88	idiov., variable	stable	complete		0.16-0.22	+	0.66	+	+
4	Veil and Codina-Altès, I[8]†	1923							idiov.	unstable	incomplete	0.20		?	0.57		
5	Veil and Codina-Altès, I[9]†	1923							idiov.	stable	complete			?			
6	Barker[10]	1926	51	M	170	−	34-42	62-77	idiov., variable	unstable	1:1 to complete	0.20	0.23-0.24	?	0.69	+	+
7	Wolferth and McMillan, I[5]	1929	60	M			28	50	suprav.	stable	complete		0.16	−	0.64-0.79‡	−	−
8	Wolferth and McMillan, II[5]	1929	37	F			29-37	56-78	idiov.	?	2:1	0.41-0.64	0.22-0.26	+	0.72	+	+
9	Wolferth and McMillan, III[5]	1929	48	F	135	−	31	90	suprav.	unstable	1:1, 2:1, complete	0.15	0.16	?	0.60-0.68‡	+	−
10	Levine[11]	1936					27	66	idiov.	?	complete		0.15	?	0.70	+	?
11	Schramm and Korth[12]	1937	52	M			27	65	suprav.	unstable	complete and incomplete	0.36	0.17-0.34	−	0.70	−	+
12	Lequime and Sanabria[13]	1937	73	M	260	−	37	94	suprav.	stable	complete		0.18-0.19	+	0.55	+ ?	+

13	Dubbs[14]	1938	72	M	160	–	24	75	idiov.?	unstable	1:1 and complete	0.24-0.32	0.13	?	0.66	+	–
14	Kline et al.[6]	1939	68	F	200		28-37	65-88	idiov., variable	unstable	1:1 and complete		0.12-0.14‡	+	0.48	+	–
15	Froment et al.[15]	1939	57	M	140	–	33	72-93	idiov.	unstable	incomplete	0.16-0.18	0.20	?	0.52	+	
16	Graybiel and White[16]	1941	82	M			33	84	idiov.	stable	complete		0.15	–	0.68	+	+
17	Bain, I[17]	1941	67	M	190	–	26	75	idiov., variable	stable	complete		0.16-0.18	?	0.68	+	
18	Bain, II[17]	1941	67	M	200	–	27-37	71-88	idiov., variable	unstable	2:1, complete	0.22-0.26	0.16	?	0.58	–	
19	Kisch and Zucker[18]	1942	64	M	120	–	24-41	60-91	idiov.	stable	complete		0.14-0.20	?	0.60	+	
20	Katz[2]	1941, 1943	50	M	150		26-29	70-75	idiov.	stable	complete		0.15-0.17	+	0.63	+	+
21	Parkinson, I	1941					27	79	idiov.	?	complete		0.13-0.15	?	0.60	+	–
22	Parkinson, II	1941					25	67	idiov.	?	complete		0.38	?	0.84	+	–
23	Winternitz and Langendorf, I	1941	62	F	200	–	27-37	73-92	idiov. and suprav.	unstable	2:1, incomplete, complete	0.205-0.26	0.15	+	0.57-0.62	+	+
24	Winternitz and Langendorf, II	1941	76	M	220		22-53	48-85	idiov.	stable	complete		0.11-0.22	+	0.64-0.87‡	–	+
25	Winternitz, and Langendorf, III	1941	48	M	150	–	29-32	40-59	suprav.	unstable	1:1 and complete	0.17-0.20	0.15-0.17	?	0.85	+	–

*P′ = P due to retrograde response.
†The cases published in 1923 are obviously those mentioned in the monograph in 1928, and are quoted only once.
‡On different days.

some of them, intraventricular block was present in addition to A-V block, in which event a rhythm originating above the bifurcation of the bundle would imitate a tertiary origin.

6. Retrograde conduction time ranges from 0.10 to 0.23 second, and was less than 0.18 second in nineteen out of the twenty-five cases. With the shortest P-P′ it may be prolonged to 0.38 second. Thus, in the majority of cases, V-A conduction is well within normal limits as compared with normal A-V conduction. In most cases of incomplete A-V block, retrograde conduction takes place more readily than orthograde conduction, as evidenced by a considerably shorter R-P′ than P-R in these cases. However, it should be realized that the relative speed of orthograde and retrograde conduction is not always indicated by the relative length of P-R and R-P′, for these two intervals do not measure the time required by the impulse to cover the same distance. This is particularly true when the ventricular pacemaker is in the A-V node.

7. The occurrence of retrograde conduction and the duration of R-P′ depend on the preceding P-R distance. The shortest P-R (0.32 second) which permitted subsequent retrograde conduction was observed in the case of Kline, Conn, and Rosenbaum.[6] Thus, the manifestation of retrograde conductivity in A-V block requires that the auricular rate be not too rapid. The sum of the shortest P-R (0.32 second) and the average R-P′ (0.18 second) gives a duration of 0.50 second, corresponding to a rate of 120/minute as about the shortest P-P distance (fastest auricular rate) that will permit a retrograde P wave. With a P-P distance of 0.49 second or less, the normal orthograde impulse will preclude the occurrence of an auricular response to a retrograde impulse.

Table IV shows the main observations in all published cases. It includes a case of Dubbs,[14] which we believe represents another instance of retrograde conduction, although the author does not comment upon this, one of Lequime and Sanabria,[13] described by them as an instance of complete block with independent auricular and ventricular rhythm, and one of Levine.[11]

RETROGRADE CONDUCTION IN A-V BLOCK

The obvious relationship between retrograde conduction and the preceding auricular pause has been considered by several authors (Daniélopolu and Danulesco[3] and others) as a manifestation of the refractory period of the auricles. However, no evidence has been presented for this assumption. The refractory period of the auricles is known to be short, and there is no evidence of intra-auricular block in the majority of such cases. Furthermore, in our second case, some auricular extrasystoles occurred after much shorter P-P intervals than those which seem to prevent retrograde conduction. The sinoauricular impulses not only stimulate the auricles, but travel down through the A-V node and the bundle of His until they reach the depressed region, which they fail to pass. Our second case demonstrates clearly that it is the state of the junctional region of depression or block, and not of the auricle, which

determines whether retrograde transmission will occur or fail. As pointed out before, the earliest retrograde response which occurred after an upright P (due to a normal or extrasystolic auricular impulse with positive P) was preceded by a definitely longer P-R than that of the earliest retrograde response which came after an inverted P (due to a retrograde response or supraventricular escape). This observation, which is inexplicable on the basis of the refractory period of the auricle, can be readily explained by the mechanism indicated in the diagram of Fig. 6.

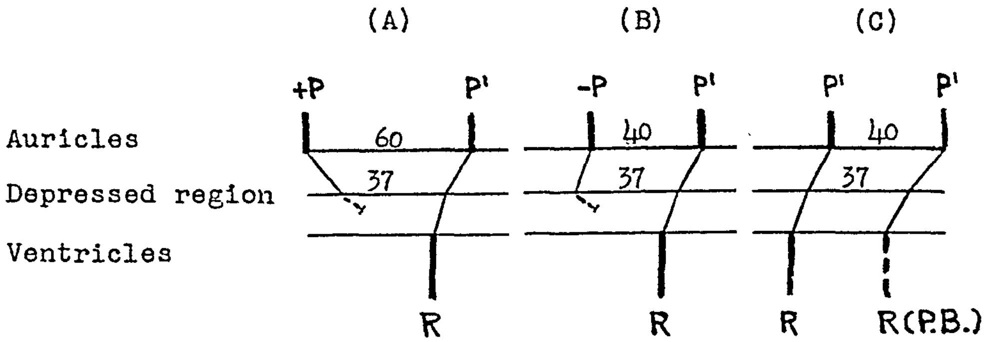

Fig. 6.—Case 2. Diagram to illustrate the relation between the recovery period for retrograde conduction and the manifest interauricular period. Time in 1/100 second.

Retrograde conduction after (*A*) orthograde P (+P), (*B*) P of a supraventricular escape (−P), (*C*) P of retrograde conduction (P′).

The earliest possible retrograde conduction after an upright P occurs at a P–P′ which is much longer than the P′–P′ of the earliest retrograde conduction after an inverted P. P–P′ includes the additional time required both by the impulse from above to reach the depressed region and by the impulse from below to travel from the depressed region to the auricle.

Two conclusions are warranted from this analysis: first, that the actual refractory period in all cases is shorter than indicated by the shortest P-P′ interval, the difference ranging from 0.2 to 0.3 second, as can be seen from Table II; and, second, that the orthograde and retrograde impulses must travel for a certain distance along the same pathway.

The paradox of normal retrograde response in cases of high-grade auriculoventricular block has puzzled all observers, and various theories have been advanced to explain it. Cohn and Fraser[7] hesitated to assume that the premature, inverted P waves were due to conduction in a reverse direction. The explanation they put forward was that the auricles were mechanically stimulated by the ventricular action. Wilson and Robinson,[8] in 1918, believed that the ventricular beats promote the discharge of auricular extrasystoles, and compared this phenomenon with the peculiar ventriculophasic sinus arrhythmia in A-V block. Later investigators discarded the mechanical theory, which is also considered unsatisfactory by Parkinson[10] and Katz.[2] In fact, it fails to explain some of the principal features of the arrhythmia, e.g., the close relation between the preceding auricular pause and the following R-P′. The analogy to the sinus arrhythmia of A-V block does not seem to be close, for the latter is of common occurrence, whereas inverted P waves are exceptionally rare, if found at all, in partial block without escaped beats. Furthermore, in several cases of the group of A-V block with V-A response, a ventriculophasic sinus arrhythmia was not present.

Barker,[10] on the basis of animal experiments[20] in which a sudden increase in intraventricular pressure was found to cause a premature beat, assumed that ventricular contraction mechanically stimulates some focus in the bundle above the supposed lesion, provoking a premature beat which is then conducted to the auricles by the normal path. The chief objection to Barker's theory, previously also raised by Wolferth and McMillan,[5] is that the interval R-P', which measured only 0.10 second in a case of Cohn and Fraser and 0.11 second in our Case 2, is too short to cover Barker's double mechanism.

Daniélopolu and Danulesco[3] were the first to suggest retrograde conduction as an explanation for inverted P waves in A-V block. Since orthograde conduction was completely absent in their cases, they assumed that retrograde transmission took place by pathways other than the bundle of His. Scherf and Shookhoff[21] refer to animal experiments[22] which showed that, under certain circumstances, parts of the conduction system of the frog's heart may allow orthograde conduction, whereas, in other parts, only retrograde conduction is possible. Schramm and Korth[12] suggest the bundle of Kent as a possible pathway for retrograde conduction. Our evidence, we believe, is opposed to this theory, for both forward and retrograde impulses appear to use the same path (Fig. 6).

The heart in one of the cases of Wolferth and McMillan[5] was examined histologically, and destruction of about ⅞ of the diameter of the bundle of His was found. The authors concluded from the localization and conical shape of the lesion that the orthograde impulse had to travel through a slightly damaged area before reaching the major obstacle. Thus, the weakened impulse was unable to overcome the latter, whereas the retrograde impulse traveled first through the major lesion in an unattenuated condition and then passed the minor obstacle as well. This theory of unidirectional block, which is similar to Mines'[23] explanation of unidirectional block as due to asymmetrical decremental conduction in a depressed region, has found strong support in the experiments of Ashman and Hafkesbring,[24] who succeeded in producing unidirectional block by asymmetrical compression of a tortoise heart muscle strip. Rothberger[25] calls the explanation of Wolferth and McMillan[5] credible, but hypothetical.

A thorough histologic examination of the conduction system was also reported in the case of Lequime and Sanabria.[13] Like Wolferth and McMillan,[5] the authors found the lesion near the bifurcation of the bundle. In addition, there was complete interruption of both bundle branches which may have occurred after the electrocardiogram was taken.

An autopsy was performed in the case illustrated in our Fig. 5, by Dr. Maurice Lev and Dr. Otto Saphir at the Michael Reese Hospital (Chicago), and we are indebted to them for permission to publish the report of the post-mortem examination.

The heart weighed 375 grams. The epicardium and endocardium were smooth and glistening. The endocardium covering the basilar portion of the left ventricular aspect of the muscular ventricular septum was dis-

tinctly depressed and grayish white in color. The valvular apparatus presented no abnormality. The myocardium of the left ventricle measured 1.1 cm. in thickness. On section it was grayish red, with many irregular, grayish-white streaks. The myocardium of the muscular ventricular septum beneath the membranous portion, on section, presented an irregular, whitish-gray, depressed area, measuring 2.5 cm. in greatest dimension. This extended throughout the whole thickness of the septum in this region. The myocardium of the right ventricle measured 0.2 to 0.3 cm. at the pulmonic orifice, 0.2 to 0.3 cm. at the tricuspid orifice, and 0 to 0.1 cm. at the left lateral margin. Both the right and left ventricular chambers were dilated. The lining of the coronary arteries presented moderate sclerosis, but the lumina were not encroached upon. The aorta also showed moderate sclerosis.

Histologic examination of the myocardium revealed a mild and, in areas, moderate, diffuse increase in young connective tissue cells. The myocardial fibers showed no remarkable changes. The small arteries showed some intimal thickening. The subepicardial fat involved the myocardium of the right ventricle.

Serial sections through the base of the muscular ventricular septum revealed the following: The A-V node and all but the most distal part of the common bundle showed no changes. At the point of giving off of the left bundle branch, the fibers were apparently interrupted by a large amount of connective tissue. This connective tissue had replaced much of the myocardium of the base of the muscular ventricular septum, and corresponded to the white area noted grossly. This connective tissue extended to the endocardium of both the right and left ventricles, and numerous connective tissue interruptions were obvious in the upper part of the right and left branch of the bundle. The fibers of these branches that remained were markedly eosinophilic and granular. The arteries showed slight intimal thickening.

The cardiac diagnosis was: (1) Localized area of fibrosis of the myocardium of the base of the muscular ventricular septum, with involvement of the distal portion of the bundle of His and both bundle branches; (2) moderate fibrosis of the myocardium elsewhere; (3) moderate coronary sclerosis; and (4) hypertrophy and dilatation of the right and left ventricles.

The abnormalities in this case are not unlike those of Wolferth and McMillan, and a similar explanation could be applied. However, the data are still not complete enough to assume that this is the mechanism. Retrograde conduction in A-V block may be more frequent than we assume, for retrograde conductivity cannot be excluded just because no premature, inverted P waves are recorded in short strips or because single observations are made in a case of A-V block. It seems significant that several observers, once their attention was drawn to the phenomenon of retrograde conduction in A-V block, were able to find other examples in their material. It is our impression that, on sufficiently close observation, a large proportion of cases of incomplete and unstable A-V block of arteriosclerotic origin will display unimpaired retrograde conduction.

Schramm and Korth[12] raise the possibility that different impulse strength might account for differences in orthograde and retrograde conduction. However, the quality of the impulse does not seem to play a decisive role, for ventricular extrasystoles are conducted to the

auricles with the same ease as idioventricular impulses of tertiary or A-V nodal origin[3, 5, 9] (and our Cases 2 and 3). On the other hand, auricular extrasystoles and supraventricular escapes are blocked out in the same way as are sinus impulses (our Case 2).

Kline, Conn, and Rosenbaum[6] made an ingenious attempt to explain the phenomenon by assuming a supernormal recovery phase, as first described in cases of incomplete A-V block by Lewis and Master.[26] Kline, et al., assumed that stimulation of the auricle promoted a supernormal phase of conduction in either direction. This explanation will not account for our Case 2. Here, with arrhythmic auricular action, orthograde impulses may be blocked in early auricular diastole, whereas retrograde impulses may be transmitted in late auricular diastole.* Kisch and Zucker[18] point out that the recovery curve constructed in their case is not of the type expected with a supernormal phase. Like Kline, et al., Froment, Masson, and Gonin[15] published a case of supernormal recovery phase, together with another case of retrograde response in A-V block; but these authors do not comment upon the possibility of a supernormal recovery phase phenomenon in the latter case.

In summary, neither the mechanical or extrasystolic hypothesis, nor the hypothesis of different pathways for orthograde and retrograde conduction, nor the assumption of a supernormal recovery phase is able to explain the facts in a satisfactory way. We are led to the conclusion that the same fibers of the specialized muscular tissue which are unable to conduct orthograde impulses are able, at the same time, to conduct in reverse direction.

This condition, although puzzling, is not without analogy in the pathology of human arrhythmias. Typical examples of A-V dissociation with interference (Mobitz's "Interferenz-dissoziation") are due to a higher rhythmicity of the A-V node, and A-V conduction is otherwise undisturbed. The laws of interference-dissociation can be applied to the arrhythmia of A-V block with V-A conduction, if the direction of conductivity is reversed. The analogy of the two conditions is shown in Table V. Thus, the arrhythmia under discussion may be called *interference-dissociation between ventricle and auricle.*

Mobitz[27] explained the retrograde block in his cases by a lack of excitability of the auricles in response to retrograde impulses, with V-A conduction, as such, unimpaired. A similar explanation could be put forward for A-V block with normal V-A conduction. With normal conductivity in either direction, a lack of response in the ventricles to normal orthograde impulses would have to be assumed. Although we feel that the analogy between Mobitz's arrhythmia and that which we are dealing with is not merely accidental, we cannot accept his explanation, which has already been criticized by Scherf and Shookhoff[21] and Scherf,[28] among others.

*On one occasion an idioventricular beat which gave rise to a retrograde P occurred more than 1.6 second after the retrograde P of a preceding ventricular extrasystole. The same record showed retrograde conduction after a P-R of only 0.28 second.

TABLE V

	INTERFERENCE-DISSOCIATION (MOBITZ)	A-V BLOCK WITH PRESERVED V-A RESPONSE
Auricular rate	Slower than ventricular rate	Faster than ventricular rate
A-V conduction	Normal, failing only after short R-P intervals	Grossly impaired or absent
V-A conduction	Absent	Normal, failing only after short P-R intervals
Conduction time	Normal or prolonged, dependent upon preceding R-P	Normal or prolonged, dependent upon preceding P-R
Type of "captures"	Ventricular	Auricular
Digitalis	May induce complete A-V block	May induce complete V-A block

Discussed in text.

We must content ourselves with the statement that orthograde and retrograde conductivity are different functions of the conducting system which may be impaired independently in the arrhythmia under discussion, as in other cases of ectopic impulse formation, both in man and experimental animals.

SUMMARY AND CONCLUSIONS

1. Three cases are described in which A-V block of various degree and stability occurred while conduction of ventricular impulses to the auricles was normal.

a. Case 1 showed unstable, occasionally complete, orthograde A-V block of arteriosclerotic origin. Retrograde conduction occurred in late auricular diastole only, and was followed by a compensatory pause. This proves that the retrograde impulses failed to reach the sinus node. Orthograde conduction, when present, was slower than retrograde conduction. Auricular fusion beats were present, resulting from simultaneous orthograde and late retrograde invasion of the auricles.

b. Case 2, observed over a long period of time, showed complete A-V block as a result of arteriosclerosis. Digitalis in average doses produced complete retrograde block, followed later, as the effect of the drug subsided, by a lengthened refractory period and a prolonged retrograde conduction time. The occurrence of ventricular extrasystoles and of A-V nodal escapes permitted a special study of the refractory period for retrograde conduction. Evidence is presented that retrograde conduction does not depend on the preceding auricular pause, but upon the recovery time of the depressed region within the A-V conducting system after the impulse invades it. The actual duration of the refractory period of this area is considerably shorter than the shortest interval (P-P′) between a normal P wave and a retrograde one: it equals the shortest P′-P′ of two retrograde responses in succession if they have the same R-P′. The variations of the refractory period over long intervals were inconsiderable. The retrograde impulse, in this case, reached the sinoauricular node, for no fully compensatory pause was present. Auricular fusion beats were present, as in Case 1.

c. Case 3 showed unstable, sometimes complete, A-V block, with normal retrograde response that was confined to ventricular impulses, as in Case 1. Intraventricular block was present in addition to A-V block. Orthograde conduction, when present, was slower than retrograde conduction. Ventricular extrasystoles were conducted to the auricles with the same ease and with the same R-P′ intervals as automatic ventricular beats of supraventricular origin. The pause after retrograde conduction was fully compensatory.

2. The electrocardiograms of two additional patients and that of one other patient, with autopsy report, are reproduced.

3. Nineteen cases of A-V block with V-A response from the literature, some of them hitherto unrecognized as cases of unidirectional block, are reviewed.

4. Retrograde excitation of the auricles gives a definite pattern of the retrograde P waves. The retrograde P is always inverted in Leads II and III, but may be upright or diphasic in Lead I; frank inversion in Lead I was not seen in our own nor in most of the published cases. Similarly, as a rule, the retrograde P in Lead I of extrasystoles or escaped beats is not inverted.

5. The different explanations which have been offered for the phenomenon of premature, inverted P waves in A-V block are reviewed. The assumption of an extrasystolic origin is rejected, as well as the thesis that A-V and V-A conduction pass along different pathways. Neither can a supernormal recovery phase be accepted as the explanation of the condition.

6. The phenomenon is regarded as a special, but by no means rare, type of incomplete heart block, and represents the reverse of Mobitz's interference-dissociation. Orthograde and retrograde conduction are considered as distinct functions of the special muscular tissue; they may be impaired separately or together, as shown by clinical observation and animal experiment.

7. The common feature in the three cases in which histologic examination of the conduction system was carried out is the absence of significant changes in the A-V node and upper part of the common bundle, whereas marked degenerative changes were present near the bifurcation of the common bundle, with involvement of the upper portions of one or both bundle branches. If this peculiar localization of the lesion is responsible for unidirectional block, the arrhythmia described may be of value in localizing the lesion of the A-V conduction system in cases of high-grade or complete A-V block.

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CARDIOVASCULAR DYNAMICS IN PATIENTS WITH ANGINA PECTORIS

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MOST physicians feel that the fundamental cause of angina pectoris is, largely or entirely, disease of the coronary arteries, and, accordingly, many studies have been made of the function of the coronary arteries and myocardium in patients with angina pectoris. There are, however, few physiologic data on the status of the circulation as a whole in this syndrome, and it was therefore considered desirable to record measurements of the general cardiovascular dynamics in patients with severe angina pectoris, uncomplicated by congestive failure, cardiac arrhythmia, or valvular disease.

MATERIAL AND METHODS

Twenty-two patients with a history of angina pectoris, but with no signs or symptoms of congestive failure, cardiac arrhythmia, or valvular disease, were studied. They ranged in age from 42 to 65 years; four (Cases 7, 10, 18, and 19) were less than 50 years of age, and three (Cases 16, 17, and 21) were more than 60 years old. Six (Cases 2, 3, 5, 8, 12, and 15) were women.

All measurements were made with the patient in the postabsorptive state, under basal conditions, after a rest of one-half to one hour; no attacks of angina occurred during any of the studies. Two different methods were employed in measuring the cardiac output: the acetylene method was used in Cases 1, 2, and 3, and the ethyl iodide method in Cases 4, 5, and 6. Studies by means of the acetylene method were made with the patient in a semirecumbent position; the basal metabolic rate was measured in duplicate first, utilizing a Collins-Benedict-Roth spirometer; calculations were made by means of the Aub-DuBois normal standards. The pulse rate was then counted twice, after which, two measurements of the arteriovenous oxygen difference were made according to the technique of Grollman, Friedman, Clark, and Harrison.[1] The minute volume output of the heart was calculated from the arteriovenous oxygen difference and the oxygen consumption; the latter was estimated from data obtained during the measurement of the basal metabolic rate. When measurements were made by means of the ethyl iodide method, the technique of Starr and Gamble[2] was used, and the oxygen consumption and basal metabolic rate were measured by the Tissot method simultaneously with the minute volume output of the heart; the patient was in a semirecumbent position. After the cardiac output was estimated by either method, the venous pressure was measured with the patient recumbent, using the method of Moritz and von Tabora,[3] after which the circulation time was measured with sodium dehydrocholate.[4] The vital

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Received for publication April 5, 1943.

capacity was then measured with a spirometer. Arterial pressure was estimated from time to time, using a mercury manometer with the standard cuff.

CASE REPORTS

CASE 1.—A 53-year-old retired storekeeper had a history of substernal squeezing pain beginning sixteen years previously. At first the pain occurred only occasionally, but its frequency increased, particularly in the preceding two years, so that, at the time of the present study, walking 100 yards regularly brought it on. It also occurred occasionally when the patient was at rest, and sometimes it awoke him from sleep. Initially the pain radiated to both arms, but, following myocardial infarction, ten months previous to this study, the radiation extended down the trunk to the legs and up into the jaws. The pain was often associated with a choking sensation, dizziness, and palpitation. There was no history of congestive failure.

Physical examination was negative except for moderate obesity, generalized arteriosclerosis, some increase in the anteroposterior diameter of the chest, occasional coarse crackles at the lung bases, and moderate cardiac enlargement. The blood pressure was 115/85.

Laboratory Studies.—The urine was negative, with a maximal specific gravity of 1.028. The erythrocyte count was 5,300,000, with a hemoglobin of 80 per cent. The leucocyte count was 9,100, with a normal smear and differential count. The fasting blood sugar was 99, nonprotein nitrogen 33, and cholesterol 297, mg. per cent. The stool was normal. The blood Hinton and Kahn reactions were negative. Electrocardiogram showed normal rhythm, rate 100, left axis deviation, P-R interval 0.20 second, notched, widened, and slurred QRS waves, prominent Q_2 and Q_3, and depressed S-T. Roentgenograms of the heart showed a transverse diameter of 17.3 cm.; the chest was 30.9 cm. in diameter; the left ventricle was prominent. The basal metabolic rate was –15 per cent.

CASE 2.—A 57-year-old housewife had a history of hypertension; this was discovered twenty years previously, when she sought medical advice because of headaches and dizziness. The past history also revealed gaseous distension for years, and nocturia for two years. Four years before the present study, she had an attack of severe, persistent, prostrating precordial pain, radiating to the back, left shoulder, and left hand, and requiring morphine. Another similar attack occurred a month later, this time with the development of dyspnea and râles in the chest, both of which were only transitory. A third severe attack, followed by transitory pericarditis and paroxysmal auricular fibrillation, occurred three years before the present study, and was followed by ten months of bed rest because of ten to twelve daily, mild attacks of pain in the precordium, neck, jaw, ear, left shoulder, and left arm. These decreased in frequency after that time to three to five a week, at which level they remained. A year before the present study, palpitation began to occur with the pain. Six months later an attack of fever, with cough and knifelike pleuritic pain, occurred, and left her with a slight cough. Two months before the present study, the fourth severe attack of precordial pain was noted. There was no history of congestive failure.

Physical examination was negative except for moderate cardiac enlargement, generalized arteriosclerosis, an apical systolic murmur, a few coarse crackling râles, and a snapping aortic second sound. The blood pressure was 160/90.

Laboratory Studies.—The urine showed a maximal specific gravity of 1.032. Mild glycosuria was present, but the urine was otherwise normal. The erythrocyte count was 5,400,000, with a hemoglobin of 80 per cent. The leucocyte count was 8,600, with a normal smear and differential count. The stool was normal. The blood nonprotein nitrogen was 19, and the fasting blood sugar ranged between 161 and 292, mg. per cent. The blood Kahn and Hinton reactions were negative. Electrocardiogram revealed normal rhythm, rate 85, left axis deviation, prominent Q_1, deep S_2, and flat T_1. Roentgenogram of the heart revealed a transverse diameter of 14.5 cm.; the chest was 24.2 cm. in diameter; the left ventricle was prominent. The basal metabolic rate was −3 per cent.

CASE 3.—A 57-year-old housewife had a family history of hypertension, a past history of nocturia for years, hypertension of seven years' known duration, and a cholecystectomy two years before the present study. Six years previously she first noted the onset of a squeezing precordial pain, associated with a choking sensation, and radiating into the left upper arm, which was brought on by exertion, excitement, or exposure to cold, and was relieved by rest and nitroglycerin. These attacks greatly curtailed her activity. Six months before this study she had a severe, prolonged attack, requiring morphine. Following this, the mild attacks became more frequent, extended over the entire chest, and radiated down both arms. There was no history of congestive failure.

Physical examination was negative except for generalized arteriosclerosis, slight cardiac enlargement, a basal systolic murmur, and a healed right upper quadrant scar. The blood pressure was 160/100.

Laboratory Studies.—The urine was negative, and showed a maximal specific gravity of 1.032. The erythrocyte count was 4,500,000, with a hemoglobin of 80 per cent. The leucocyte count was 9,000, with a normal smear and differential count. The stool was normal. The fasting blood sugar was 82, the nonprotein nitrogen 35, and the cholesterol 260, mg. per cent. The blood Hinton and Kahn reactions were negative. Electrocardiogram showed normal rhythm, rate 70, left axis deviation, depressed $S\text{-}T_{1,2,4}$, elevated $S\text{-}T_3$, inverted T_3, and inverted P_3. Roentgenogram of the heart revealed a transverse diameter of 13.8 cm.; the chest measured 27.8; the left ventricle was prominent and, on fluoroscopy, showed evidence of infarction; the aorta was somewhat calcified. The basal metabolic rate was −11 per cent.

CASE 4.—A 59-year-old tailor had had nocturia for several years. Five years before the present study, he first noted the appearance of a burning sensation above the left elbow, not associated with anything at all; this disappeared after six months. Six months later it recurred, this time associated with a similar pain in the left upper arm and a squeezing sensation in the chest and upper abdomen, all brought on by walking 100 yards. The pains were more frequent in winter, but averaged about ten a day through the year. Six months before the present study, the pain became more frequent and severe, so that dressing, eating, and moving about in bed brought it on; it was commonly associated with a feeling of shortness of breath when precipitated by more prolonged exertion. He used 2,200 nitroglycerin tablets during this six-month period. In addition, in the three and one-half years preceding the present study, he had noted pain in the calves, which was worse in winter, brought on by walking and relieved by standing still.

Physical examination was negative except for moderate obesity, arteriosclerosis, an increase in the anteroposterior diameter of the chest, slightly prolonged expiration, an apical systolic murmur, moderately cold and cyanotic feet, and poor arterial pulsations in the feet. The blood pressure was 150/100.

Laboratory Studies.—The urine was negative, and showed a maximal specific gravity of 1.030. The erythrocyte count was 4,850,000, with a hemoglobin of 75 per cent. The leucocyte count was 8,000 with a normal smear and differential count. The stool was normal. The fasting blood sugar was 93, and the nonprotein nitrogen was 34, mg. per cent. The blood Hinton and Kahn reactions were negative. Electrocardiogram revealed normal rhythm, rate 75, left axis deviation, depressed S-T_1, inverted T_1, and deep S_2. Roentgenogram of the heart showed a transverse diameter of 14.7 cm.; the chest measured 30.0 cm.; the left ventricle was prominent and the aorta tortuous. The basal metabolic rate was –4 per cent.

CASE 5.—A 56-year-old housewife, whose father died of heart disease and one of whose sisters had hypertension, had a history of frequent sore throats in childhood, mastoidectomy at 20 years of age, hysterectomy at 44 years of age, intolerance of fatty foods for years, and pains in the large joints for eight years. Four years before the present study, she was troubled with nosebleeds and frontal headaches and was found to have hypertension. A short time later she began to experience a sense of painful pressure in the precordium, spreading to the left shoulder and arm, and occasionally to the scapula, precipitated by a walk of 250 to 300 yards, or by climbing up a flight of stairs. It was worse in cold weather, associated with a feeling of inability to catch her breath, lasting a few minutes, and followed after its disappearance by soreness over the precordium. Although her activities were considerably limited, she was able to do her housework. There was no history of congestive failure.

Physical examination was negative except for moderate obesity, arteriosclerosis, slight enlargement of the heart, and Heberden's nodes. The blood pressure was 150/90.

Laboratory Studies.—The urine showed a maximal specific gravity of 1.018; albumin and sugar were not detected, but occasional erythrocytes and leucocytes were noted in the sediment. The erythrocyte count was 4,750,000, with a hemoglobin of 80 per cent. The leucocyte count was 7,800, with a normal smear and differential count. The stool was normal. The fasting blood sugar was 125, the nonprotein nitrogen, 39, and the cholesterol 297, mg. per cent. The blood Hinton and Kahn reactions were negative. Electrocardiogram showed normal rhythm, rate 70, left axis deviation, deep S_2, and notched QRS_3. Roentgenogram of the heart showed a transverse diameter of 13.8 cm.; the chest measured 27.7 cm.; the left ventricle was prominent. Graham test showed poor filling of the gall bladder. The basal metabolic rate was –2 per cent.

CASE 6.—A 56-year-old unemployed man, one of whose brothers had heart disease, had a history of gonorrhea forty years previously, and had been partly deaf for some years. Seven years before the present study, he suddenly experienced a tearing sensation to the left of the sternum. Since then a similar pain came on with exertion, excitement, or eating; later, it radiated to the left scapula and down the arm to the wrist, and was associated with a choking sensation. The frequency of his attacks required that he take 20 to 30 nitroglycerin tablets daily; he was bedridden

most of the time. The frequency of his attacks diminished two years before this study to about fifteen per day, requiring 100 nitroglycerin tablets weekly, and he was able to leave the house from time to time. He had occasional attacks of pain while at rest or asleep. One year before the study, a left-sided paravertebral alcohol injection from D_2 to D_5 was done; some of the thoracic manifestations of angina disappeared, but the number of attacks was not changed. After this procedure, he developed severe neuritis over the chest, and a few basal râles were noted. There was no history of congestive failure.

Physical examination was negative except for moderate obesity, generalized arteriosclerosis, an increase in the anteroposterior diameter of the chest, and a few basal râles. The blood pressure was 140/85.

Laboratory Studies.—The urine was negative, and showed a maximal specific gravity of 1.030. The erythrocyte count was 4,950,000, with a hemoglobin of 80 per cent. The leucocyte count was 8,100, with a normal smear and differential count. The stool was normal. The fasting blood sugar was 109, the nonprotein nitrogen, 32, and the cholesterol 328, mg. per cent. The blood Hinton test was negative and the Kahn test was doubtful. Electrocardiogram showed normal rhythm, rate 75, left axis deviation, deep S_2, and inverted, monophasic QRS_3. Roentgenogram of the heart showed a transverse diameter of 15.2 cm.; the chest measured 31.8 cm. The basal metabolic rate was -22 per cent.

TABLE I

CASE	CARDIAC OUTPUT (L./MIN.)	CARDIAC INDEX	ARTERIO-VENOUS O_2 DIFFERENCE (VOL. %)	CIRCULATION TIME (SEC.)	VENOUS PRESSURE (CM. H_2O)	VITAL CAPACITY (C.C.)	ARTERIAL PRESSURE (MM. HG)	CARDIAC ENLARGEMENT
1	3.3	1.9	5.85	22	3.5	2350	115/85	+
2	2.7	2.0	5.95	18	8.0	1600	160/90	+
3	3.7	2.1	5.00	18	6.0	1750	160/100	+
4	3.8	2.0	6.15	16	8.1	2800	150/100	0
5	3.8	2.2	5.80	13	9.1	--	150/90	+
6	3.5	1.8	5.60	20	3.8	2800	140/85	0
7	--	--	--	19	8.0	3600	140/95	0
8	--	--	--	17	4.2	2000	165/95	0
9	--	--	--	22	10.9	3750	110/70	+
10	--	--	--	17	9.7	3600	145/85	0
11	--	--	--	15	5.7	--	115/75	0
12	--	--	--	16	4.6	2200	180/110	0
13	--	--	--	19	3.4	2500	170/120	+
14	--	--	--	21	--	3300	140/80	0
15	--	--	--	17	8.4	2900	145/80	+
16	--	--	--	15	5.0	2650	130/80	0
17	--	--	--	13	3.2	--	120/70	0
18	--	--	--	14	5.0	3400	160/100	0
19	--	--	--	17	3.5	3500	190/100	+
20	--	--	--	16	--	2850	140/80	0
21	--	--	--	16	7.2	3850	180/90	0
22	--	--	--	21	3.4	4100	160/110	0

OBSERVATIONS

The cardiac index was within the normal range[5] of 2.2 ± 0.3 liters/minute/square meter of body surface in five of six instances; the apparently low value in Case 6 was associated with a basal metabolic rate

of –22 per cent. The arteriovenous oxygen difference was within normal limits in every case.

Values for circulation time were within the normal range of 12 to 19 seconds in all but five patients (Cases 1, 6, 9, 14, and 22). Three of these (Cases 1, 6, and 14) had basal metabolic rates at or below –15 per cent, and a fourth (Case 9) had polycythemia vera.

Normal values for venous pressure were found in all patients.

The arterial blood pressure was at or above 150/90 in about half the cases. In most instances the elevations in blood pressure were slight.

A decrease in vital capacity, usually slight, was found in all instances but one (Case 22).

DISCUSSION

In 1935, Starr and Gamble,[6] summarizing their studies with the ethyl iodide method, stated that the cardiac output was normal in patients with angina pectoris. Later, Bazett, et al.,[7] using a method based on pulse wave velocity, reported a normal cardiac output in one patient (Case 9 of their series) with uncomplicated angina pectoris. The results of the present study are in accord with these earlier observations: the volume and velocity of the circulation are normal. Somewhat slowed circulation times, associated with low metabolic rates, were found in three patients of the present study, including one whose cardiac index was also slightly decreased. Another patient with somewhat slowed velocity of blood flow had polycythemia vera. It is concluded that the slight slowing of blood flow seen in a few instances was due to metabolic or other noncardiac factors. Bernstein and Simkins[26] also observed that angina pectoris does not affect the circulation time. The low vital capacities of most of our patients are to be ascribed to age, obesity, and a short, stocky build, rather than to pulmonary congestion, for no signs or symptoms suggestive of the latter were detectable. The only common abnormality in cardiovascular dynamics was a slightly elevated arterial blood pressure in half of the patients; a similar incidence of hypertension has been reported by other authors.[8]

It is difficult to reconcile the observations on cardiac output and circulation time described in the past by other authors, as well as those reported here, with the recently published results of Starr and Wood.[9] These authors, using the ballistocardiograph to estimate cardiac output, found normal values in only five patients with angina pectoris, and low values in nineteen, including fifteen whose cardiac output was 30 to 60 per cent below normal. Four of the latter group developed congestive failure while under observation, but no such complicating factor was present in the others. Accordingly, other explanations must be invoked to explain the markedly subnormal cardiac output in these patients. One criticism of studies of the minute volume output of the heart by means of the ballistocardiograph is that they afford no information on the relation of the volume of the cardiac output to the metabolic require-

ments of the body. The utility of expressing cardiac output in terms of oxygen consumption was recognized by even the earliest authors.[10-12] Later workers have also emphasized the parallelism between metabolism and circulation, Grollman,[5] by relating the latter to surface area, and Starr, et al.,[13] by again pointing out its relation to oxygen consumption. It is clear, therefore, that the value of data on cardiac output is impaired by the absence of corresponding data on metabolism; this is especially true in patients with angina pectoris, since many of them have low metabolic rates.[8] The weight of the evidence appears to favor the conclusion that, except for arterial hypertension in many, the general circulation is normal in relation to metabolic requirements at rest and in the absence of anginal pain in patients with angina pectoris. It is apparent, therefore, that studies of this sort afford no explanation as to the mechanism of the occurrence of angina.

The anatomic cause of angina pectoris, namely, disease of the coronary arteries or their ostia, has been clearly defined.[14] In everyday life, attacks of angina pectoris commonly occur at times when the cardiac output is increased, i.e., during exertion or emotional upsets, or after heavy meals. Starr, Donal, and Collins[15] found that the cardiac output was increased in two patients during attacks of angina which were precipitated by emotion in one, and by the injection of epinephrine in the other. Both the former[16] and the latter[17-20] factors have been shown to increase cardiac output. It is not valid, however, to conclude that attacks of angina pectoris are in every instance associated with increased cardiac output. For instance, sympathomimetic amines, such as paredrine, which elevate blood pressure but do not increase cardiac output,[20] may cause anginal pain in patients with a history of angina pectoris.[21] It is clear from the formula of Evans and Matsuoka,[22] $W = OP + \frac{wV^2}{2g}$*, that an increase either in cardiac output or in blood pressure increases the work of the heart, and accordingly it may be concluded that the occurrence of angina pectoris is usually related to increased cardiac work. On the other hand, angina may occur when the work of the heart is not increased, i.e., during exposure to somewhat reduced atmospheric oxygen tensions,[23] or even when cardiac work is actually decreased, i.e., in cardiac arrhythmias with marked tachycardia.[24] The factor responsible for angina in these situations appears to be myocardial anoxia, consequent, in the one, to inadequate oxygenation of arterial blood, and in the other, to inadequate flow through the coronary tree which results from shortening of diastole. A valid generalization based on physiologic data is a reaffirmation of the clinical con-

*W — Work.
O — Output per minute.
P — Mean blood pressure.
w — Weight of blood.
V — Velocity of blood in aorta.
g — Gravitational constant.

cept that factors which increase cardiac work or decrease myocardial oxygenation lead to angina in patients with disease of the coronary arteries or their ostia, although reflex mechanisms are also of importance in many patients.[25]

SUMMARY AND CONCLUSIONS

1. Studies of the circulation were made on twenty-two patients with a history of angina pectoris, but with no signs or symptoms of congestive failure, cardiac arrhythmia, or valvular disease.
2. The cardiac output and circulation time were normal in relation to the metabolic requirements. When slowing of the circulation occurred, it was because of noncardiac factors.
3. The venous pressure was normal in all instances.
4. The only common abnormality of cardiovascular dynamics was arterial hypertension.
5. The relation of available physiologic studies of the circulation to the occurrence of attacks of angina is discussed; it is concluded that a valid generalization based on physiologic data is a reaffirmation of the clinical concept that factors which increase cardiac work or decrease myocardial oxygenation lead to angina in patients with disease of the coronary arteries or their ostia, although reflex mechanisms are also of importance in many patients.

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CRITICAL EVALUATION OF CARDIAC MENSURATION IN THE TREATMENT OF ADDISON'S DISEASE WITH DESOXYCORTICOSTERONE ACETATE

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THE reciprocal activity of sodium and desoxycorticosterone acetate in maintaining the patient with Addison's disease has been previously demonstrated, according to the equation $Na \times D = k$, where Na represents the daily ingestion of sodium in grams, D, the daily requirement of desoxycorticosterone acetate in milligrams, and k, a constant for which, in eight patients, values between 30 and 45 have proved satisfactory.[1-4] In all of these studies, cardiac mensuration has been used as an index of the degree of sufficiency of the treatment, and it has been found that, within limits, the size of certain cardiac measurements, notably the cardiothoracic ratio, frontal cardiac area, and total cardiac volume, vary directly with the condition of the patient. In other words, as the patient improves, a concomitant increase occurs in the proportions of the abnormally small heart associated with untreated Addison's disease. This point is well illustrated in Fig. 1, in which it is shown that the cardiac measurements varied directly as the product of the amount of sodium and desoxycorticosterone acetate ingested, and the degree to which this particular patient was symptomatically controlled. Such significant observations have been duplicated to a greater or lesser degree in all of our cases.

It is our present purpose to emphasize the limitations of cardiac mensuration as a guide to the amount of desoxycorticosterone acetate and sodium which should be administered to any patient with Addison's disease at a given time.

Some 200 observations of cardiac size in thirteen patients with Addison's disease served as a basis for the study. Eight of these patients have been seen in crisis, and followed under treatment with desoxycorticosterone acetate and measured amounts of sodium for periods varying from twenty weeks to four years.

As in previous work, the cardiothoracic ratio, the frontal cardiac area (sq. cm.), and the heart volume (c.c./M^2 body surface) have been taken as indices, and averaged values have been obtained for the thirteen patients as follows: in crisis, 0.35, 84, and 314, respectively; in

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Read before a clinical session of the New York Heart Association, March 30, 1943, at the New York Academy of Medicine.
Received for publication April 15, 1943.

states of insufficiency, 0.39, 96, and 390, respectively; and in the adequately treated patient, 0.46, 122, and 480, respectively.

The cardiothoracic ratio, the frontal cardiac area, the cardiac volume, and the body surface area have been estimated by methods previously described.[1]

Criteria for the recognition of states of crisis, insufficiency, stabilization, and overtreatment have been fully given elsewhere.[1,4,5]

The ability of desoxycorticosterone acetate and sodium to alter cardiac size in a quantitative manner has definite limitations in actual practice:

1. There are faults inherent in the methods of mensuration necessarily employed in vivo. The technique of taking roentgenograms must be as nearly uniform as possible. In the present series of cases we have discarded more than seventy films as being unfit for comparison for this reason alone. Moreover, difficulty is encountered in actively delineating the frontal cardiac area, in ascertaining the actual geometric configuration of the heart, and so forth. These problems have already been discussed in greater detail.[1,4]

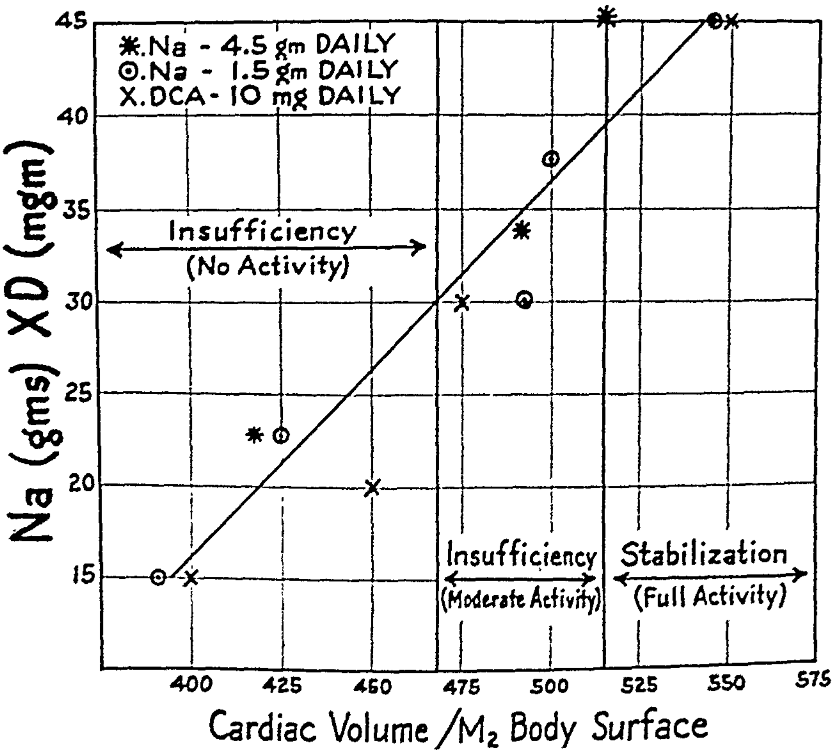

Fig. 1.—Effect of varied products of Na X D on heart size in relation to control of Addison's disease.

2. Measurements of the heart vary widely from person to person, so that no yardstick covering all cases can be made. For example, composite measurements of two patients are contrasted in Table I.

It appears inevitable that each patient must serve as his own control. If such a plan is followed, the percentual changes upward or downward in subsequent measurements have been found to correspond

TABLE I

PATIENT	C. T. R.	F. C. A.	HEART VOL./M^2 BODY SURFACE
	Crisis or Impending Crisis		
K. K.	0.26	66	236
M. C.	0.31	79	282
	Insufficiency		
K. K.	0.35	85	299
M. C.	0.39	96	367
	Stabilization		
K. K.	0.42	119	426
M. C.	0.47	125	461

roughly with the clinical condition of the patient and the degree to which the disease is controlled by sodium and desoxycorticosterone acetate.

3. When crisis is adequately treated with salt or with salt and desoxycorticosterone acetate, the size of the heart will increase rapidly until blood volume is restored. This may be accomplished entirely by the use of salt, provided a sufficient amount and concentration are given. Apparently the reduced blood volume is partly responsible for the small heart of Addison's disease, as demonstrated earlier.[1, 4]

4. Immediately after crisis has been controlled, products of sodium and desoxycorticosterone acetate much beyond 45 may be, and have been, used for considerable periods of time without producing an enlargement of the heart to critical proportions. The data in Table II are illustrative.

TABLE II

VARIATIONS IN RESPONSE TO HORMONE IN, AND IMMEDIATELY FOLLOWING, CRISIS, AS RELATED TO CARDIOTHORACIC RATIO

PATIENT	DAILY INTAKE OF		PRODUCT	NUMBER OF DAYS USED	C.T.R.	
	NA (GM.)	DCA. (MG.)			BEFORE	AFTER
E. M.	11.0	10	110	14	0.33	0.45
J. F.	3.0	15	45	21	0.38	0.39
	3.0	20	60	7	0.39	0.45
	3.0	25	75	17	0.45	0.51
H. L.	10.7	10	107	9	0.46	0.58
H. L.	2.5	25	63	19	0.40	0.52
K. G.	3.0	15	45	14	0.34	0.35
	3.0	20	60	7	0.35	0.37
	3.0	25	75	7	0.37	0.40
M. C.	4.5	15	68	12	0.31	0.36
	4.5	15	68	7	0.36	0.36
	3.1	25	75	4	0.36	0.40

It will be noted that products of Na and D varying from 60 to 110 have been used for intervals of four to twenty-one days without causing cardiac failure. The exception to this statement is Patient H. L., who received 10.7 Gm. of sodium and 10 mg. of desoxycorticosterone acetate daily for nine days, at the end of which time she developed

widespread peripheral edema and congestive cardiac failure with pulmonary edema. The great variation in response of the individual patient is still further reflected in the cardiothoracic ratios, which, in one instance (M. C.), remained stationary over a seven-day period on a sodium-desoxycorticosterone acetate product of 68. These differences in reaction cannot be attributed entirely to variations in the clinical condition of the patients, at least in so far as we are able to measure it. For the present, it seems to be important to emphasize the variation and to utilize increasing heart size in the individual case as an end point in ascertaining when and to what extent the dosage of drug and the allowance of sodium shall be changed.

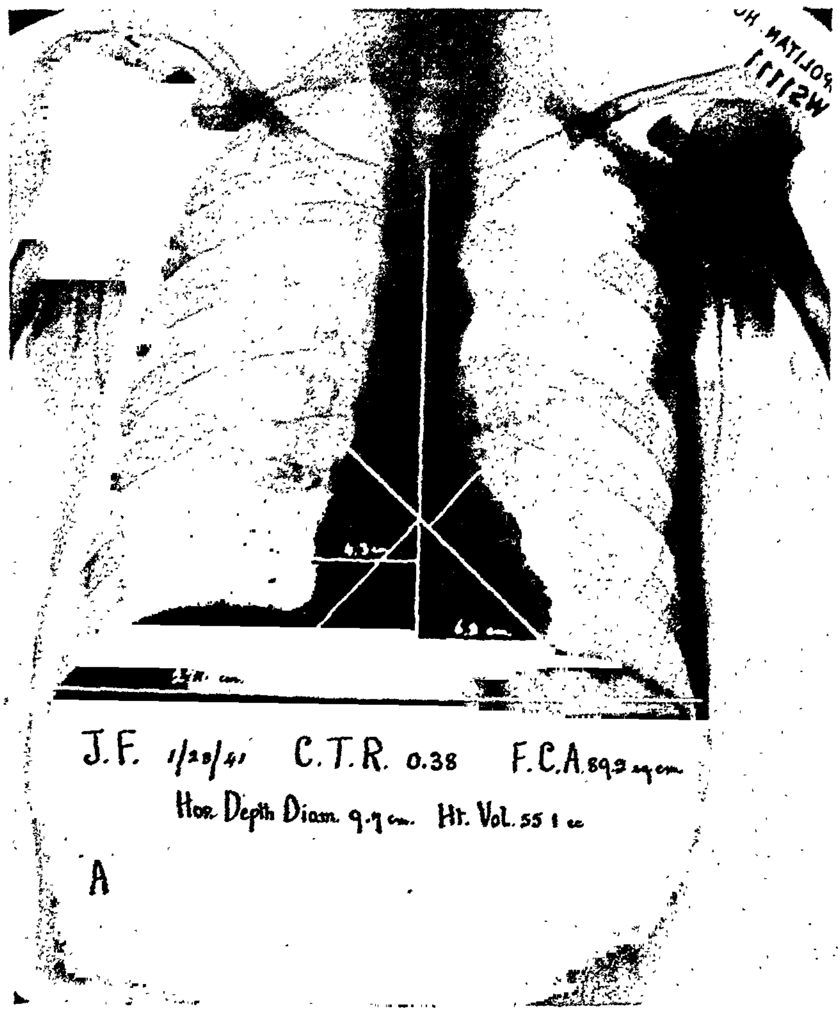

Fig. 2A.—J. F. Patient in crisis. Note the relatively large cardiac measurements as compared with Fig. 2B.

5. In two patients (J. F. and E. M.), the cardiac measurements have remained well within the normal range of values despite the onset of toxic symptoms, notably hypertension. In one of these two, very slight, transient, pretibial edema also occurred. In both instances the patients had been controlled and maintained at a sodium-desoxycor-

TABLE III

HYPERTENSION OCCURRING WITHOUT HEART FAILURE OR INCREASE IN CARDIAC SIZE

PATIENT	STABILIZED WEEKS	DAILY INTAKE OF		PRODUCT	C.T.R.*	B.P.
		NA (GM.)	DCA. (MG.)			
J. F.	18	3	15.0 S†	45	0.48	116/72
	38	5-7	4.8 P‡	75-105	0.49	210/110
E. M.	36	6	2.5 P‡	45	0.42	120/74
	90	1.5	30.0 S†	45	0.42	170/120

*C.T.R. = Cardiothoracic ratio.
†S = Oily suspension for intramuscular injection.
‡P = Pellet of crystalline material for subcutaneous implantation.

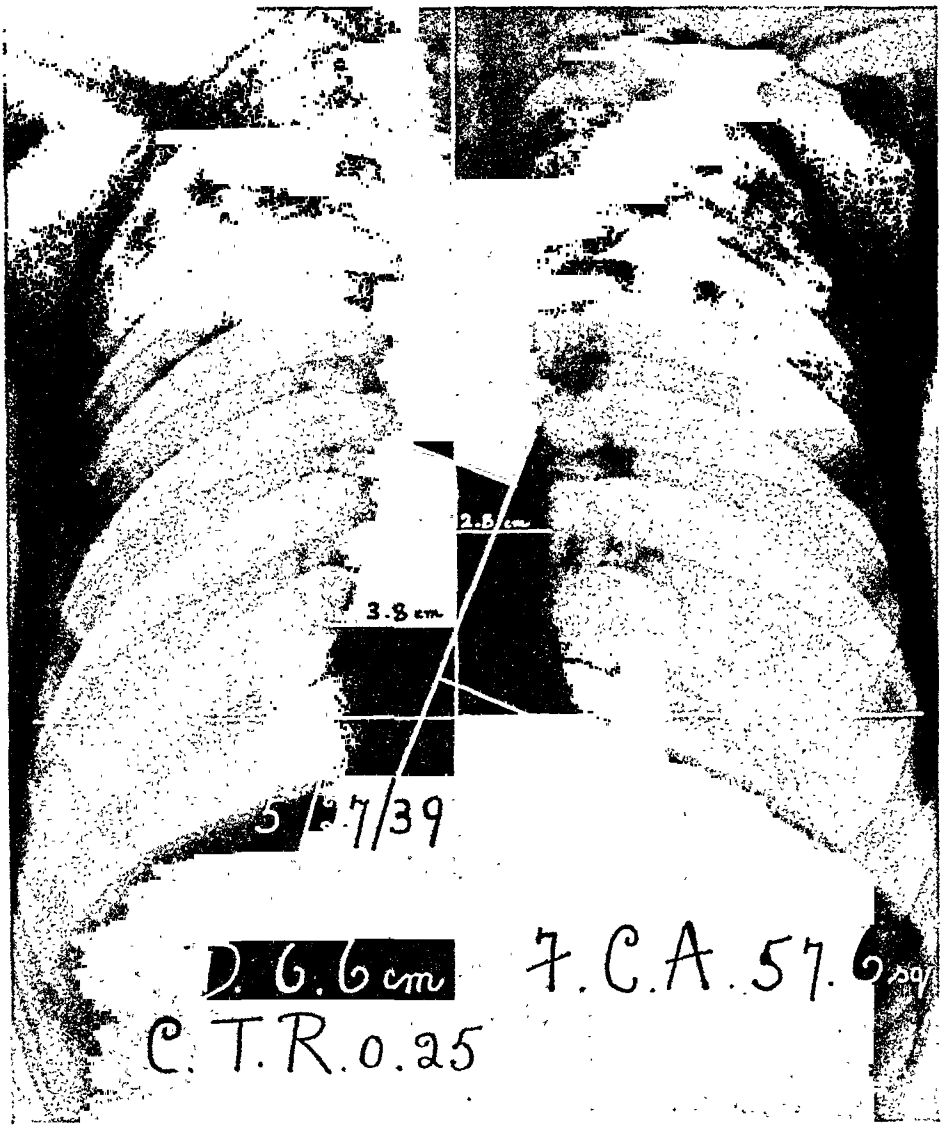

Fig. 2B.—K. K. Patient in crisis. Heart volume/M², body surface 236 c.c. Note contrast in the size of the hearts of the two patients illustrated, despite the same state of adrenal insufficiency.

ticosterone acetate level of 45 for relatively long periods of time: E. M. for 80 weeks and J. F. for 18 weeks (see Table III). In the eightieth week of treatment, E. M. was found to have changed his dietary slightly; he was ingesting approximately 3.75 Gm. of sodium instead of the prescribed 3 Gm. At the same time, he was receiving by absorption from implanted pellets of desoxycorticosterone acetate

the equivalent of 15 mg. daily of the drug by injection in sesame oil.* Inasmuch as he felt well and his cardiothoracic ratio had been long stabilized at approximately 0.42, he was allowed to continue this regime. Ten weeks later the blood pressure had risen to hypertensive levels, as noted in Table III, but the heart failed to show any evidence of further enlargement at this time. In the case of J. F., language difficulties were apparently responsible for his adding large quantities of salt to his food and not using the diet prescribed. He was not seen between the eighteenth and thirty-eighth weeks, during which time he dieted as he pleased and received, by absorption from implanted pellets, the equivalent of 15 mg. of desoxycorticosterone acetate daily by injection. From calculation of a week's menus and the rough estimation of salt intake, it is believed that he consumed between 5 and 7 Gm. of sodium daily, at least for the latter part of this period. The hypertension (210/110) was not reflected in any appreciable increase in the cardiac measurements over the period of time during which it existed. Four days after the sodium intake was regulated by using the previously prescribed 3 Gm. daily, the blood pressure fell to 120/82.

It is of special interest to note that this high product of sodium and desoxycorticosterone acetate (about 85) for a considerable period of time did not cause cardiac failure, whereas, in the earlier treatment of this patient, immediately after the relief of crisis, a ratio of 75 (3 Gm. of sodium and 25 mg. of desoxycorticosterone acetate) caused acute pulmonary edema and dilatation of the heart after daily use for two and a half weeks.

These observations lead us to the conclusion that overdosage in the well-controlled patient will not be detected early by increasing heart size, but is more likely to produce the syndrome of hypertension, with or without other concomitant phenomena, such as peripheral edema, weakness, or altered kidney function.

SUMMARY AND CONCLUSIONS

1. The changing size of the heart can be used within definite limits as an index of the respective amounts of sodium and desoxycorticosterone acetate that can be employed safely in the treatment of Addison's disease.

2. In general, cardiac measurements can be maintained within normal limits by a product of sodium in grams and desoxycorticosterone acetate in milligrams of 30 to 45; the actual figure is very constant for any individual patient.

3. In utilizing this rule, individual variations in cardiac size and errors inherent in the technical procedures for carrying out cardiac mensuration must be considered.

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*For this and all the other patients, desoxycorticosterone acetate in sesame oil for injection and as sterile compressed tablets for implantation was furnished by Dr. Max Gilbert, of the Schering Corporation, whose courtesy is herewith gratefully acknowledged.

4. This rule is not applicable to (a) patients in crisis and for short periods after the control of crisis; at such times, larger products of sodium and desoxycorticosterone may be used with relatively small upward alterations in the cardiac silhouette; (b) patients under control for long periods of time who inadvertently or purposely utilize more than the prescribed amount of either sodium or desoxycorticosterone acetate, or both, despite which the cardiac measurements may remain well within normal limits, while hypertension or other toxic symptoms appear.

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PRODUCTION OF NEPHROSCLEROSIS AND CARDIAC HYPERTROPHY IN THE RAT BY DESOXYCORTICOSTERONE ACETATE OVERDOSAGE

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SOME time ago it was found[1] that testosterone and other testoid compounds increase the size of the renal tubules and induce hypertrophy of the cells lining the parietal lamina of Bowman's capsule. Kidneys thus stimulated by testosterone are not only morphologically, but even functionally, above normal, inasmuch as they exhibit an increased resistance against the damaging effect of sublimate[2, 3] or ureteral obstruction.[4] The literature concerning this so-called "renotropic" action of the steroids has recently been reviewed,[5, 6] and hence will not be considered here in detail. Suffice it to say that, although there is no complete interdependence between the renotropic and the testoid action of steroids, generally speaking, the two tend to run parallel.

A short time ago it was found that desoxycorticosterone acetate (DCA.) causes typical nephrosclerosis, accompanied by cardiac hypertrophy and other signs of hypertension, in young chicks.[7] This nephrosclerosis is especially readily obtained in chicks which receive comparatively high doses of sodium chloride in their drinking water.[8] Mammals, on the other hand, proved particularly resistant to this effect. Moderate degrees of nephrosclerosis were produced in one experimental series in the dog, monkey, and rat, and here again sodium chloride appears to have played some part in the production of the condition, for the animals received varying amounts of sodium chloride during certain periods of the desoxycorticosterone acetate treatment.[9] This nephrosclerotic effect has not as yet been obtained with testosterone or any other testoid compound. It appears to depend upon the corticoid action of steroids, and, up to the present, has been detected only in desoxycorticosterone acetate, progesterone, and acetoxypregnenolone, whose nephrosclerosis-producing effect, as well as their corticoid potency, decreases in the order in which they are here mentioned. In view of the great clinical importance of nephrosclerosis and hypertensive heart disease, it appeared worth while to develop an experimental technique which would reliably produce such changes in mammals by overdosing them with adrenal cortical compounds. The object of the present communication is to report on such additional experiments,

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Received for publication April 16, 1943.
*Work performed during a tenure of a Canadian National Research Council Studentship.

which revealed that marked cardiac hypertrophy and nephrosclerosis are readily produced in the rat by a suitable combination of desoxycorticosterone acetate and sodium chloride overdosage.

EXPERIMENTAL

Twenty male albino rats, weighing 76 to 105 grams (average 92 grams) at the onset of the experiment, were divided into two groups of ten each. The animals of the first group received 10 mg. of desoxycorticosterone acetate per day in two subcutaneous injections; the compound was administered in the form of a fine aqueous crystal suspension containing 50 mg. per cubic centimeter. This treatment was continued throughout the experiment, but, after ten days of desoxycorticosterone acetate administration, the drinking water of both groups was substituted by a 1 per cent sodium chloride solution. Thus, the administration of salt was identical in the experimental and control groups, but only the former received desoxycorticosterone acetate. Treatment with this steroid was continued for a period of two months, during which time seven of the injected animals succumbed with signs of marked nervous disturbances. Most of them showed varying degrees of tremor and hyperirritability, and, in some of them, certain muscle groups became paralyzed. This was particularly obvious in one rat, which became quite unable to move the extensor muscles of one forepaw. Similar nervous disturbances in animals receiving desoxycorticosterone acetate in combination with sodium chloride have been described previously,[9] but since they are not very relevant to the problem under discussion, we do not propose to discuss them here in more detail. It is noteworthy, however, that all the animals which succumbed during the experimental period showed varying degrees of nephrosclerosis and cardiac hypertrophy. These lesions were even more pronounced in the three surviving animals, which were autopsied at the end of the two-month treatment period.

The most striking change observed in the desoxycorticosterone acetate group was an enormous enlargement of the kidneys, the surface of which was mottled and rather irregular (Fig. 1). A cross section through the kidneys, viewed at low magnification (Figs. 2 and 3), revealed that the renal papilla remained normal in size and the medulla showed only slight structural abnormalities, whereas the cortex was approximately twice as wide as that of the control animals, and exhibited great irregularities due to patches of sclerosis, obstruction of tubules by casts, etc. Under higher magnification, in many instances, wedge-shaped areas of dense sclerosis were noticeable (Fig. 4). Throughout the kidney, most of the glomeruli were sclerosed. The tuft capillaries exhibited marked hyalinization, and masses of proliferating epithelioid cells surrounded the glomeruli. The stroma was infiltrated by small round cells, or consisted of thick bands of dense connective tissue. The frequently dilated tubules contained many hyaline casts

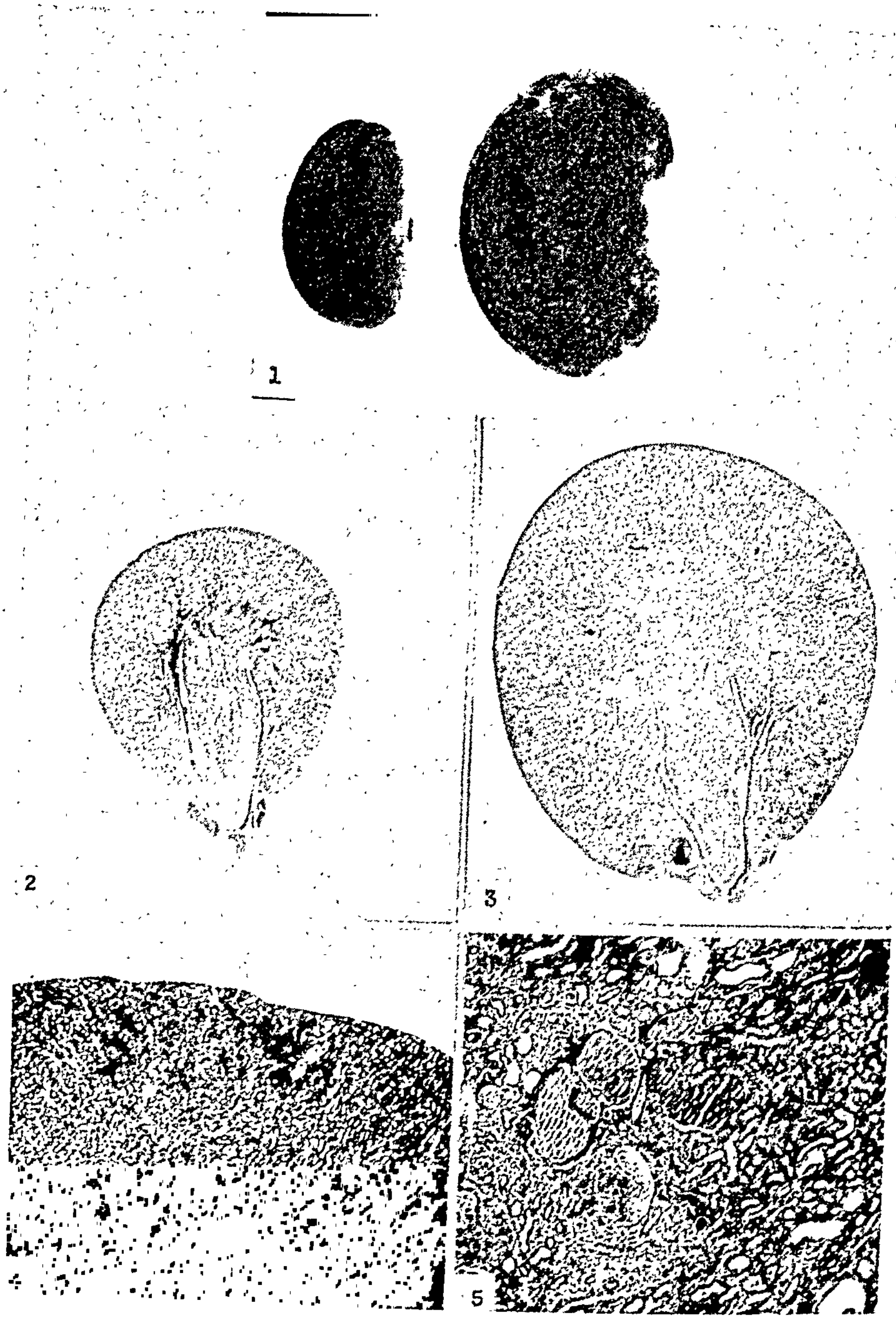

Fig. 1.—Macroscopic view of normal kidney of animal which received sodium chloride only (left), and greatly enlarged, mottled kidney of animal which received sodium chloride plus desoxycorticosterone acetate (right).

Fig. 2.—Low magnification view of cross section through kidney of normal rat which received sodium chloride only.

Fig. 3.—Low magnification view of cross section through kidney of animal which received sodium chloride plus desoxycorticosterone. Note that the renal papilla is approximately normal in appearance, whereas the cortex is greatly enlarged and exhibits an irregular pattern due to dilatation of cast-filled tubules and patches of sclerosis.

Fig. 4.—A V-shaped sclerotic area in the renal cortex of a desoxycorticosterone acetate treated rat.

Fig. 5.—Several dilated renal tubules containing hyaline casts and one sclerotic glomerulus surrounded by epithelioid cell proliferations. Same animal as that shown in Fig. 4.

(Fig. 5). Frozen sections stained with sudan III revealed lipid depositions in the proximal convoluted tubules and in many of the sclerotic glomeruli, as well as in a few of the casts. Some of the medium-sized arterioles were likewise rich in lipid granules and showed marked proliferation of the fibromuscular elements of their walls. In general, the appearance was that of the "large white kidney" in the process of being transformed into the nephrosclerotic kidney, although the secondary contraction of the organ had not progressed far enough to compensate for the initial enlargement.

The heart was likewise greatly enlarged in all the desoxycorticosterone acetate treated animals, and, on cross section under low

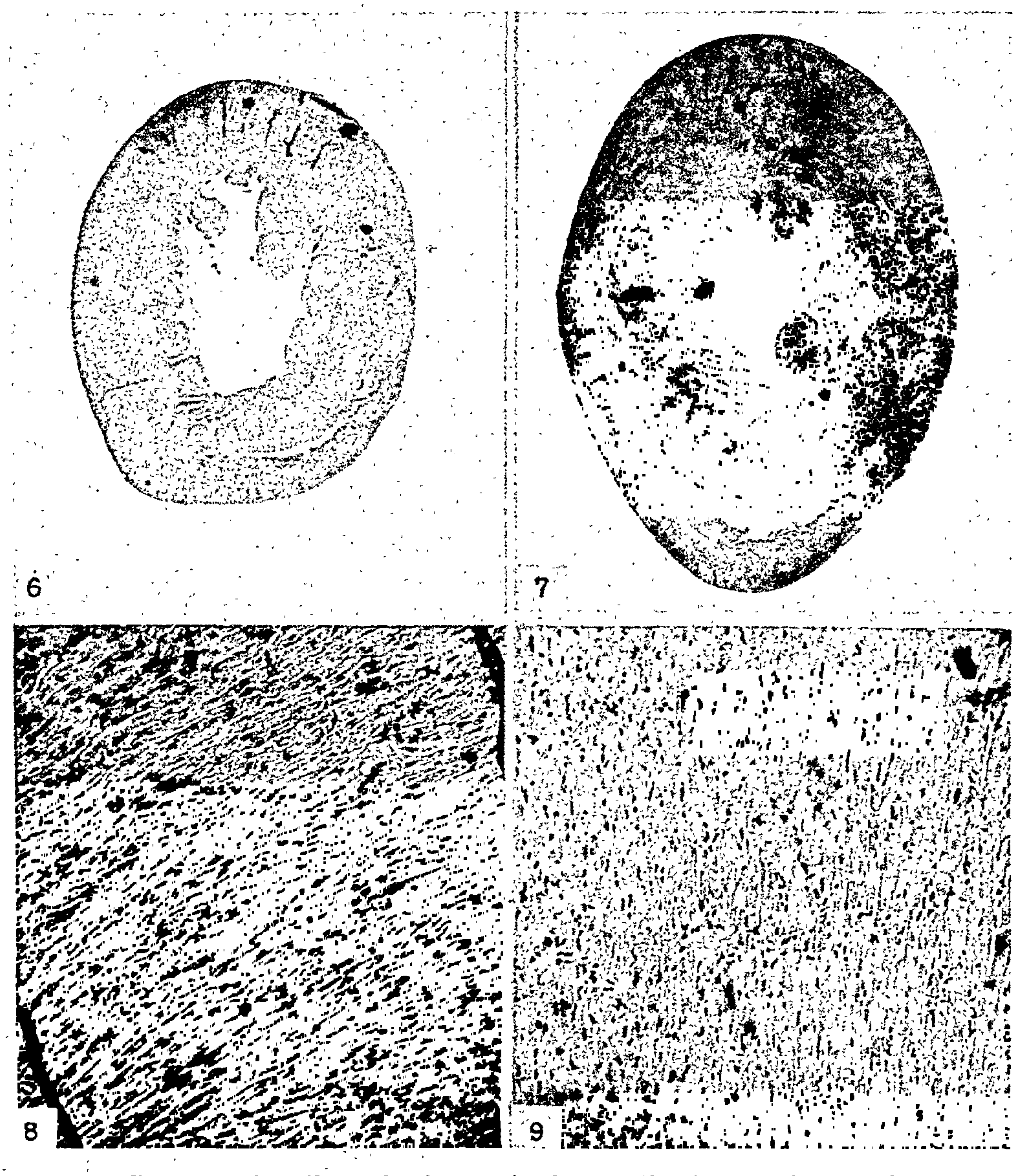

Fig. 6.—Cross section through the ventricles of the heart of normal control rat which received sodium chloride alone.

Fig. 7.—Cross section through the ventricles of the heart of a rat which received sodium chloride plus desoxycorticosterone acetate. Same magnification as Fig. 6. Note the great increase in the thickness, especially of the left ventricle.

Fig. 8.—High magnification of a section through the left ventricle of the heart shown in Fig. 6.

Fig. 9.—Section through the left ventricle of the heart shown in Fig. 7. Same magnification as Fig. 8. Note the great increase in the width of the muscle fibers.

magnification, it appeared that both the right and the left ventricles partook in this hypertrophy, although the change was much more obvious in the latter (Figs. 6 and 7). Under high magnification (Figs. 8 and 9), it became evident that the enlargement of the heart was not due merely to edema, but was caused by actual increase in the width of the individual fibers. The enlargement of the heart and kidneys is even more striking if we consider that the body weight of the desoxycorticosterone acetate treated animals was far below normal because treatment interfered with their normal growth. Table I gives the average body and organ weights (with the range in brackets) of the desoxycorticosterone acetate treated and control animals at the end of the experiment, that is to say, after two months of treatment. It will be noted that, since seven of the desoxycorticosterone acetate treated animals died earlier during the experimental period, the weights of these had to be eliminated from the averages because they were not comparable to the remaining treated and the control rats, all of which were killed on the same day.

TABLE I

EFFECT OF DESOXYCORTICOSTERONE ACETATE ON ORGAN AND BODY WEIGHTS OF RATS SENSITIZED BY SODIUM CHLORIDE ADMINISTRATION*.

	CONTROLS	DCA. TREATED
Body weight	226 (185-265)	176 (145-180)
Kidneys	1.75 (1.3-2.0)	3.41 (2.9-4.4)
Heart	0.89 (0.82-1.0)	1.36 (1.34-1.37)
Spleen	1.1 (0.6-1.6)	2.49 (1.82-2.96)

*All weights are expressed in grams.

It should be emphasized that the changes which occurred in these rats could not have been due to the desoxycorticosterone acetate itself, for they were never observed in the numerous experiments performed in this laboratory with desoxycorticosterone acetate on rats which were receiving a normal sodium chloride intake. This does not mean that the steroid cannot cause any cardiorenal lesions on a normal salt intake, but merely that its effect on the above organs is greatly augmented by sodium chloride. It will be recalled in this connection that Darrow and Miller[10] noted necrosis of myocardial fibers in rats which were overdosed with desoxycorticosterone acetate and on a normal diet. Such lesions were not observed in our series. It should be emphasized also that, in the present experiments, the cardiorenal effects were not due to the sodium chloride per se, for the controls and the experimental animals received the same salt solution.

From the above experiments it appears that chronic treatment with desoxycorticosterone acetate in combination with a high sodium chlo-

ride intake causes marked renal changes and, probably as a result of the former, pronounced cardiac hypertrophy. It is suggestive to assume, therefore, that the rise in blood pressure which is known to follow desoxycorticosterone acetate overdosage in man, as well as in animals, may be secondary to the renal changes caused by this hormone. It is well to keep in mind, furthermore, that the increase in heart volume which often follows desoxycorticosterone acetate and sodium chloride treatment of patients with Addison's disease[11, 12] may be due partly, at least in chronically treated patients, to actual muscular hypertrophy and not merely to dilatation.

Our observations also indicate that adrenal cortical hyperactivity should be considered as a possible etiologic factor in the production of the so-called "renal hypertension" in man.

In the introductory section of this paper we mentioned the fact that, at least in the chick, nephrosclerosis and cardiac hypertrophy have also been produced with progesterone. Hence, it is tempting to assume that the hypertension which often develops in women during gestation may be related to the increased production of progesterone and similar steroids which is known to occur during this period. In any case, our observations give experimental support to the view that a derangement in the production or metabolism of steroids may play an important role in the pathogenesis of renal lesions that are conducive to hypertensive heart disease.

SUMMARY

Experiments on albino rats indicate that, if the sodium chloride intake is kept high, desoxycorticosterone acetate regularly produces nephrosclerosis, cast formation in the renal tubules, and hypertrophy of the renal arterioles, as well as marked cardiac hypertrophy. The significance of these observations is discussed in connection with their possible bearing on the cause of nephrosclerosis and hypertensive heart disease in man.

The expenses of this investigation were defrayed through a grant received from the DesBergers-Bismol Laboratories. The authors are also indebted to Dr. Erwin Schwenk of the Schering Corporation, of Bloomfield, N. J., who supplied the desoxycorticosterone acetate for these experiments.

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INTRAVENTRICULAR BLOCK WITH ECTOPIC BEATS APPROACHING NORMAL QRS DURATION

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THE occurrence in cases of intraventricular block of ectopic beats with ventricular complexes of normal duration or of a duration shorter than that of the sinus beat is rare. One such case was reported by Wilson and Herrmann,[1] who explained the phenomenon as follows: "The ventricular extrasystole (cycle A_2, Fig. 19) was of septal origin and reached both ventricles at about the same time, but it reached the right ventricle below the blocked area, and the form of the resulting ventricular complex is more nearly normal than that of the sequential ventricular complexes." It has been shown experimentally[2] that, in the dog's heart without intraventricular block, stimulation of the ventricular surface at the longitudinal sulcus produces complexes with normal QRS duration, whereas stimulation on either side of this region produces complexes with prolonged QRS duration.

A second case of bundle branch block with premature systoles of relatively normal form was reported by Hewlett,[3] who could offer no explanation for it other than that given by Wilson and Herrmann. In view of their frequent occurrence, Hewlett discards the idea that two stimuli arising simultaneously, one in each ventricle, could result in these premature complexes.

Because of the rarity of this phenomenon we are presenting three more such cases.

CASE 1.—Five tracings were taken on this patient over a four-year period. Sinus rhythm was present in all of them. In the second, third, and fifth records (Figs. 1, *B*, 2, *A*, and 2, *B*), alternation of the P-P interval was present without changes in P-wave contour or P-R interval. In the first and fifth records (Figs. 1, *A* and 2, *B*), QRS was of normal duration (0.09 second) and of similar contour in corresponding leads. The third (Fig. 2, *A*) and fourth (not shown) records revealed intraventricular block of the common type, with a QRS duration of 0.16 second. The second record (Fig. 1, *B*) showed sinus rhythm with intraventricular block of the same type as in the third and fourth records, and, in addition, showed beats with a normal QRS duration which resembled those in the first and fifth (Figs. 1, *A* and 2, *B*) records. These apparently normal beats were seen in Leads II and CF_2, although in the latter only one such beat was present. In Lead II the first normal QRS was a premature systole, and the second followed at an R-R in-

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Aided by the A. D. Nast Fund for Cardiovascular Research.
Received for publication March 17, 1943.

terval which was longer than that of the regular sinus rhythm. The second normal QRS was preceded by a P wave with a P-R interval of 0.16 second, which was 0.01 second shorter than that of the regular sinus beat. After a normal sinus beat, the sequence was repeated. The duration of QRS in these beats was 0.10 and 0.08 second, as opposed to 0.16 second for the QRS duration of the sinus beat with intraventricular block.

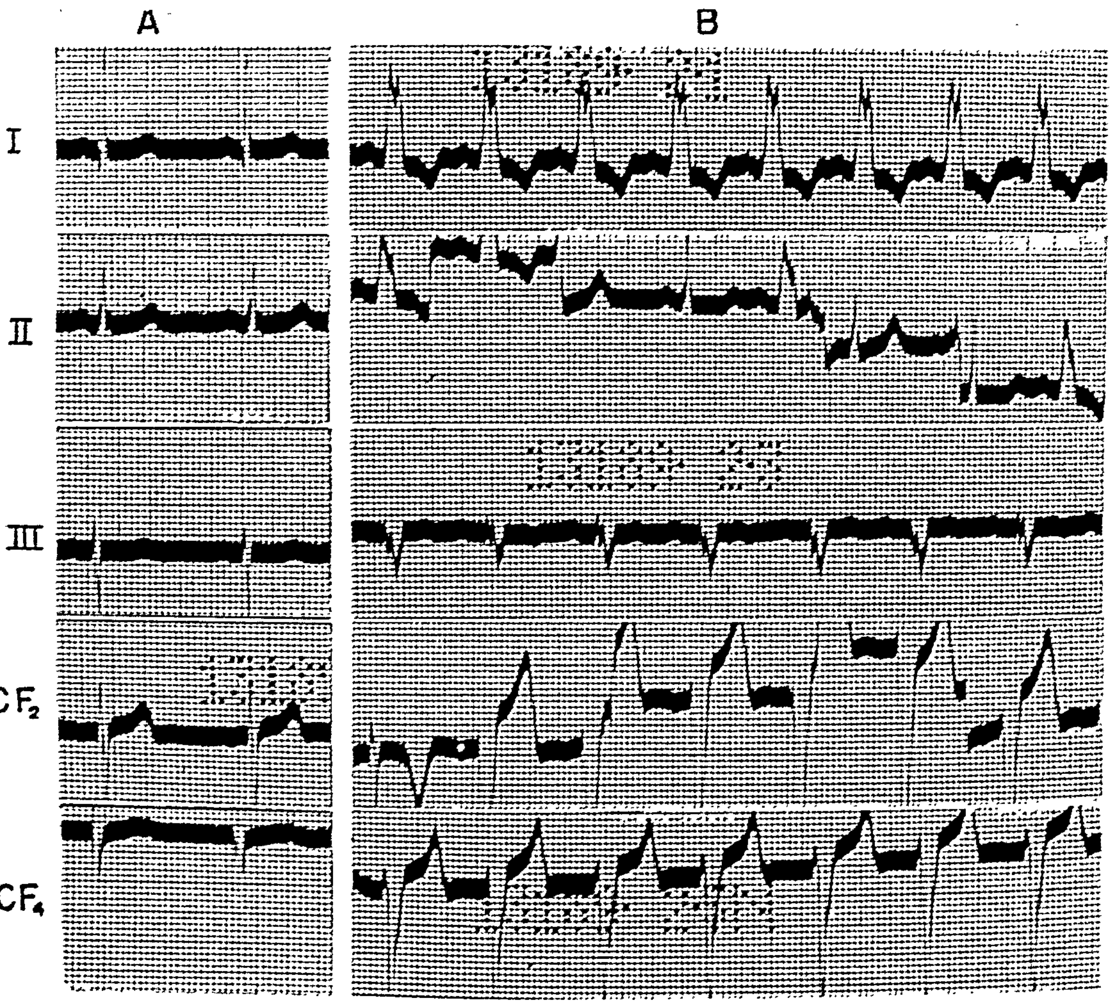

Fig. 1.—Case 1. Described and discussed in text.

The normal QRS duration of the premature beats in these records in the presence of intraventricular block can be explained in two ways: (1) by a certain localization of the site of ectopic impulse formation in relation to the region of bundle branch block,[1,2] or (2) by a supernormal phase of recovery within the injured tissue, i.e., the region of intraventricular block. If the impulse arises within the septum at a point approximately equidistant from the two bundle branches, and enters the two bundle branch systems below the region of block, reaching both the right and left ventricles at the same time, the resulting QRS would appear normal in contour and duration. That this may have happened here is plausible because the QRS of the premature beat and the one following resemble in contour the beats of supraventricular origin in the control records (Figs. 1, *A* and 2, *B*). If, on the other hand, the

impulse arose above, instead of below, the region of block, presumably in the A-V node, and reached the region of block in the bundle branch system in the supernormal phase of recovery, so that it was conducted without delay, then a QRS of normal contour and duration would result.

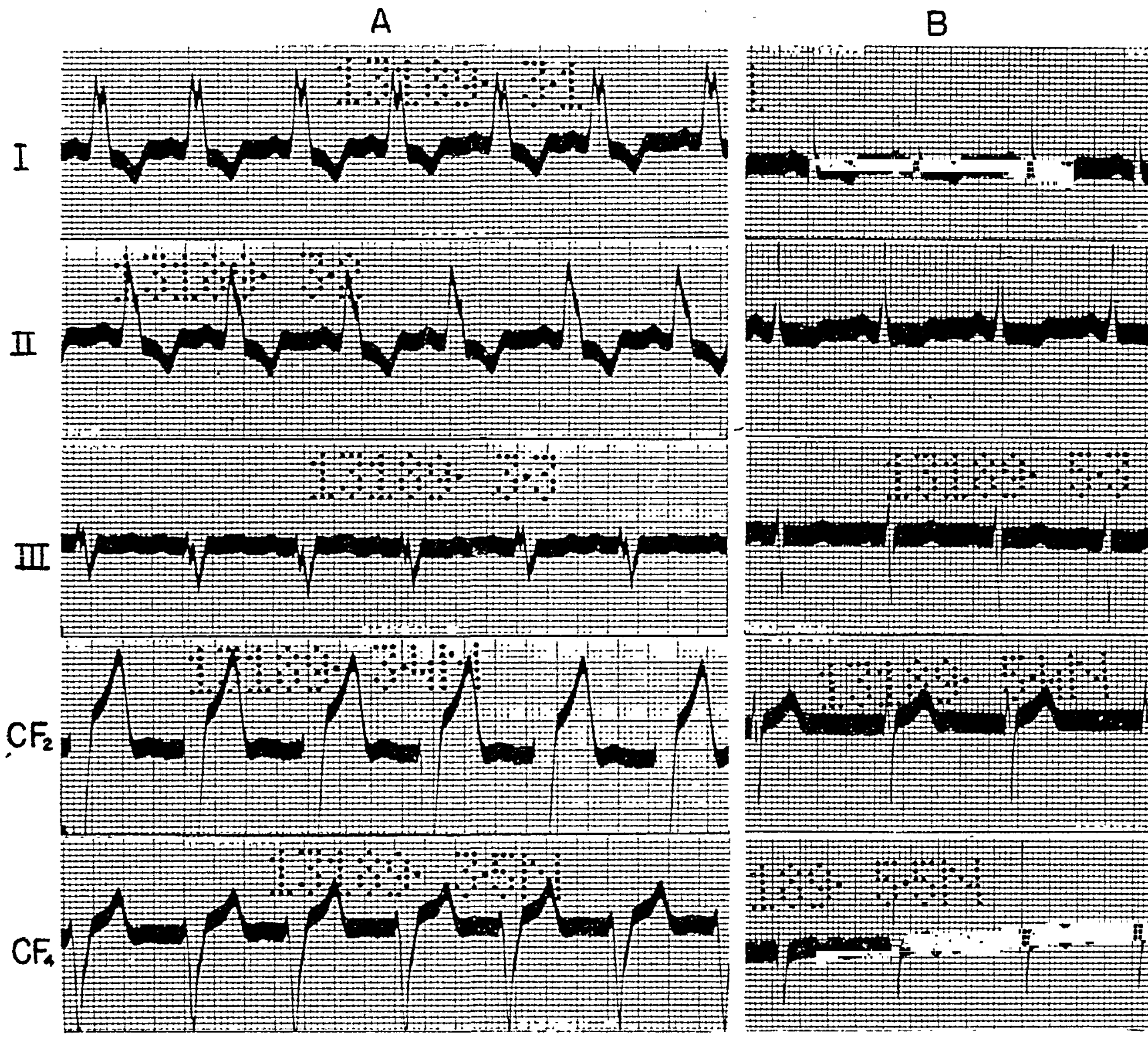

Fig. 2.—Case 1. Described and discussed in text.

The explanation of the second normal QRS invokes further mechanisms which were not considered in the explanation of the premature beat. It might, of course, be a second discharge from the same ectopic focus which gave rise to the premature beat. However, because the P-R of this second normal QRS is almost that of the normal sinus beat with intraventricular block, it is possible that this is a normally conducted sinus beat which arrived enough later in the injured tissues after the preceding impulse to permit their complete recovery and hence allow normal conduction. This presupposes that the block is reversible. Alternatively, the second beat with normal QRS duration may actually be a fusion beat. If this is the case, the impulse from the ectopic pacemaker must reach one bundle branch at the same time as the sinus impulse, and the other bundle branch before the sinus impulse reaches

or traverses the area of block. The S-T-T after the second QRS of normal duration was intermediate in contour between the S-T-T associated with the QRS of intraventricular block and that of the first QRS of normal duration; this lends credence to the idea of a fusion beat. However, the change in S-T-T configuration may be of no moment, because it is known that S-T-T changes occur after premature systoles.

Because the configuration of the QRS-T of the premature and following beats resembled that of the QRS-T at the time of undisturbed sinus rhythm without intraventricular block, the spread of the impulse through the ventricles under both circumstances was similar. This is in agreement with our assumption that the location of the ectopic impulse is such that it reaches both bundle branches at the same time, and below the level of the region of block.

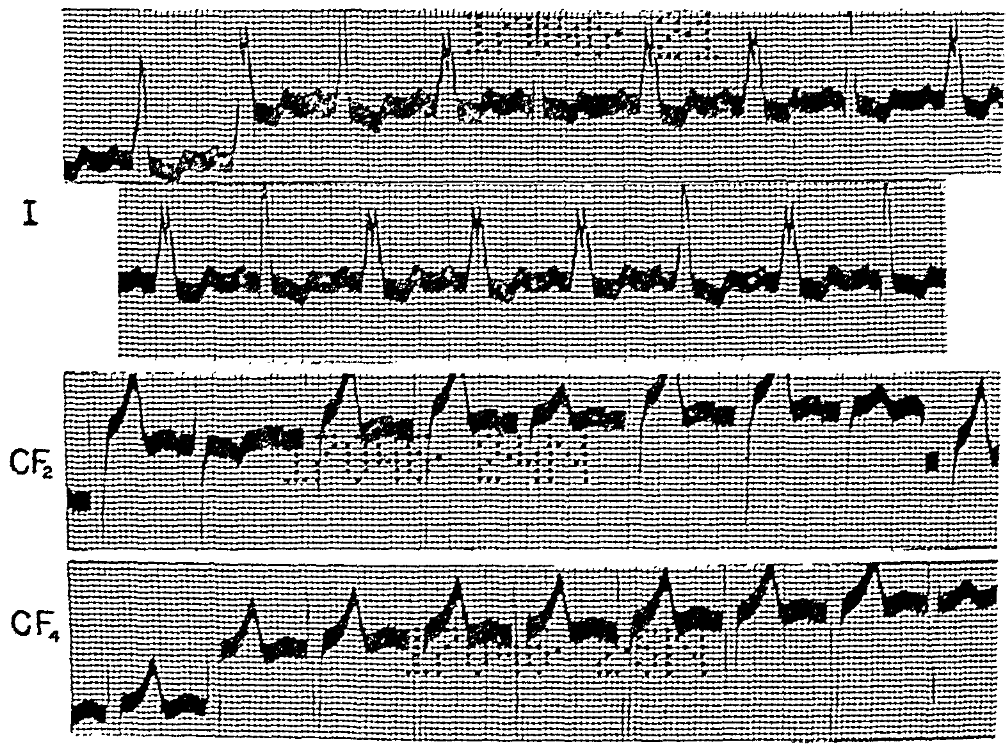

Fig. 3.—Case 2. Described and discussed in text. The first two segments are a continuous strip of Lead I.

The bigeminal rhythm which occurred in Figs. 1, *A*, 2, *A*, and 2, *B* was interpreted as due to (1) auricular premature systoles arising close to the S-A node, (2) premature systoles arising within the S-A node, or (3) alternation in S-A conduction time. The first possibility is not regarded as likely because of the identity of the P waves and P-R intervals in all beats. An exact differential diagnosis between the two remaining possibilities cannot be made; therefore, unless one wishes to assume alternation in S-A conduction, this would be an example of premature systoles arising within the sinus node. Ordinarily, the diagnosis of premature systoles of sinus origin is difficult to make, but in this instance the regular recurrence of the premature beats makes their recognition more definite.[4]

Case 2.—Five tracings were taken on this patient during an eight-month period. All five records showed sinus rhythm with intraven-

tricular block of the common type and a QRS duration of 0.16 second. The first three records showed premature systoles, not preceded by premature P waves, with a QRS duration shorter than that of the sinus beat. In the first (not shown) and third (Fig. 4) records the premature beats occurred just before, during, or after the sinus P wave, and there was a variation of as much as 0.14 second in the R-R interval of the premature beat and the preceding beat.

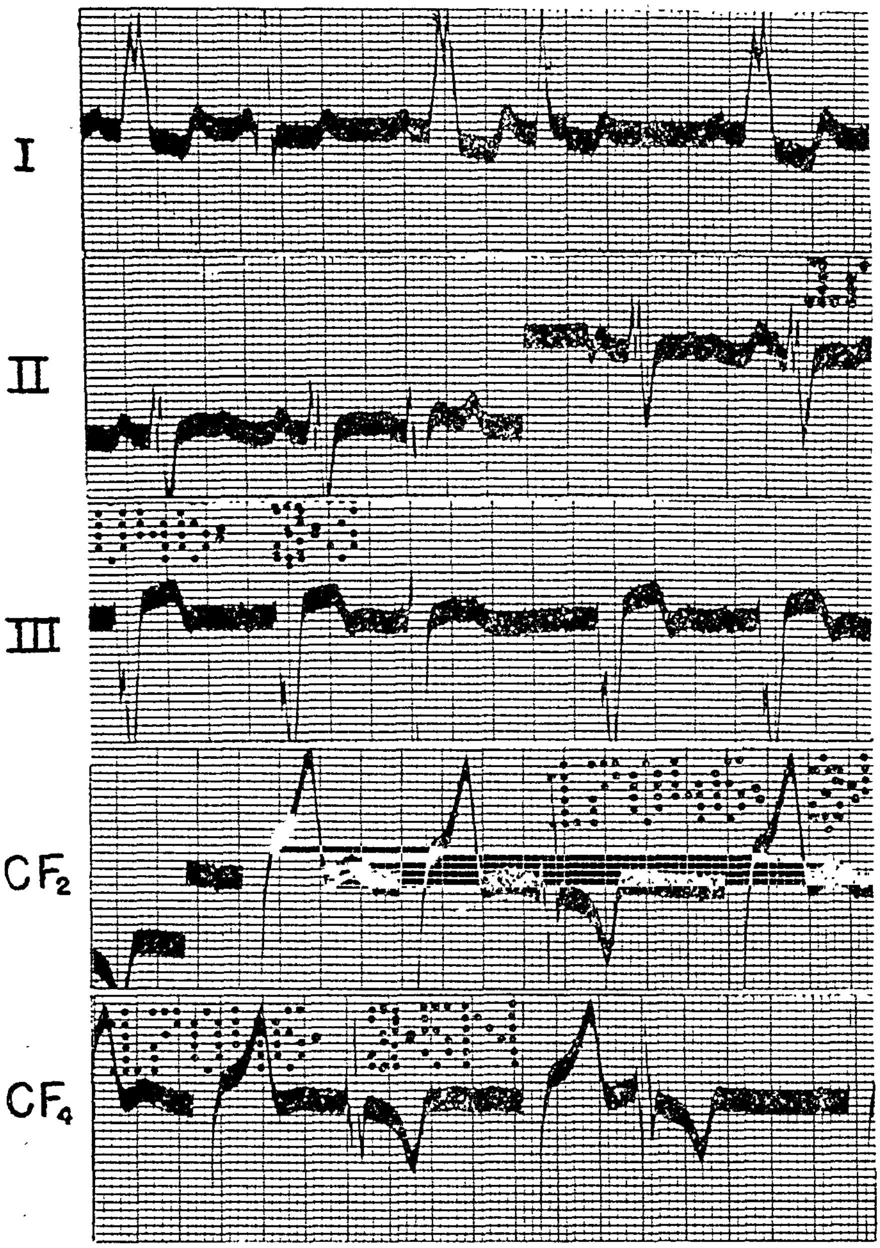

Fig. 4.—Case 2. Described and discussed in text.

In the second record (Fig. 3), of which only Lead I, CF_2, and CF_4 are available, the premature systoles occurred late in diastole and were preceded by the normal sinus P wave at a P to QRS distance which varied from 0.12 to 0.18 second. The P-R of the normal sinus beats measured 0.18, and the QRS duration, 0.16 second. The QRS duration of the premature beats varied from 0.09 to 0.13 second. The later in diastole the premature beat occurred, the longer its QRS became. This suggests that two pacemakers were controlling the heart during the time

of the premature beat. When the premature beat occurred early, the interference between the two took place above the bifurcation of the common bundle, so that the auricles were controlled by the sinus, and the ventricles by the ectopic pacemaker; when the ectopic pacemaker discharged relatively later, the interference was below the bifurcation of the common bundle, so that the ventricles were stimulated by both pacemakers and a fusion beat resulted.

The interpretation of the records in Case 2 is similar in many respects to that of the records in Case 1. The premature beats probably arose from a focus within the interventricular septum, and spread equally to both bundle branch systems below the region of block. The possibility that an ectopic focus was situated above the region of block and gave rise to impulses which passed through the injured tissues (the region of block) during the supernormal phase cannot be entertained in interpreting this series of records because the beats with normal QRS duration occurred over a variable period in the cycle, from very early to just before the expected occurrence of the sinus beat. The presence of fusion beats when the R-R of the premature beat approached that of the sinus beat, while the sinus rhythm remained regular, is further evidence that a sinus pacemaker, plus an active ectopic pacemaker, was responsible for the variations in the electrocardiogram.

It is important to emphasize that, in sinus rhythm *without* intraventricular block, the same type of septal ectopic pacemaker may be operating, giving rise to premature beats which are indistinguishable from nodal premature beats. In the presence of block in the bundle branch system it is possible, as these two cases show, to have an ectopic pacemaker so located in the ventricle that it gives rise to ventricular complexes with normal QRS duration.

CASE 3.—Two records were taken, three months apart. The first record* (Fig. 5, *A*) shows sinus rhythm with intraventricular block of the common type. The duration of QRS is 0.16 second. Premature systoles from one focus, with a QRS duration of 0.14 second, which is less than that of the sinus beat, occur throughout the tracing. Depending upon the time of the arrival of these beats in the cardiac cycle, they are either interpolated or followed by a compensatory pause. In the second record (Fig. 5, *B*), auricular fibrillation is present. Most of the ventricular complexes correspond in contour and duration to the sinus beats in Fig. 5, *A*. In addition, there are beats of shorter QRS duration. These occur at both short and long intervals after a QRS which corresponds in contour and duration to the supraventricular beat in Fig. 5, *A*. Some of the beats of shorter QRS duration resemble in contour the premature systoles of Fig. 5, *A*, and, for that reason, are considered to be of ectopic origin.

Unlike the previous cases, in this case the QRS of the ectopic beat is not of normal duration, although it is not as long as the QRS of the dominant rhythm. To explain this, we must again localize the ectopic site of impulse formation to the interventricular septum below the bifurcation of the common bundle. The explanation would then be that the impulses are originating below the region of block, but that the spread to the two bundle branches is not equal in time, and because of this, the resultant QRS shows slight prolongation.

*This is part of a record previously reproduced in Katz: *Electrocardiography*, Philadelphia, 1941, Lea & Febiger, Fig. 394.

In Fig. 5, *B,* Lead I shows ectopic complexes of two varieties, one with an upright QRS like that of left bundle branch block, and the other with an inverted QRS which simulates right bundle branch block, indicating that here we are dealing with two foci of impulse formation below the bifurcation of the common bundle and below the region which gives rise to intraventricular block of the beats of supraventricular origin; one impulse spreads more rapidly to one bundle branch, and the other spreads more rapidly to the opposite bundle branch.

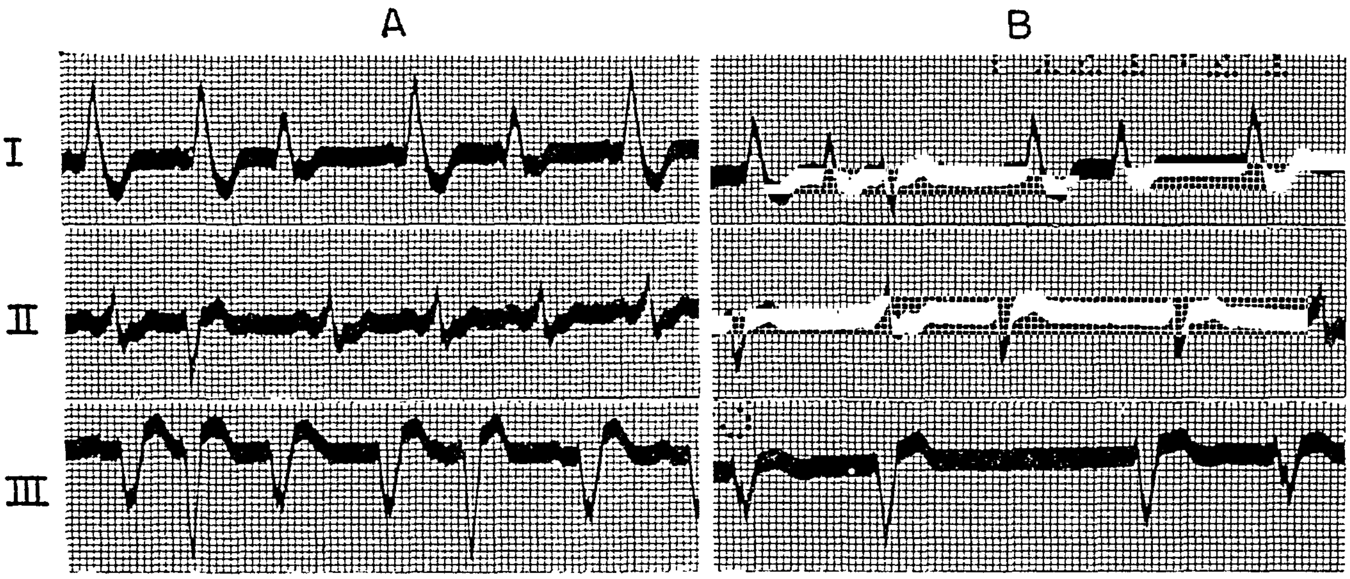

Fig. 5.—Case 3. Described and discussed in text.

That a supernormal phase of conduction is not involved in this record is proved by the second tracing, which shows the QRS of shorter duration both early and late in diastole, and shorter QRS complexes of two different types.

SUMMARY AND CONCLUSIONS

1. Three cases are presented in which ectopic beats of relatively normal contour and duration occurred during tracings of sinus rhythm with intraventricular block.

2. The explanations for these involved a consideration of (a) the site of ectopic impulse formation, and (b) the recovery phase of the region of bundle branch block.

3. The explanation offered by others,[1, 3] namely, an ectopic pacemaker situated in the interventricular septum, with equal spread to both ventricles below the region of block, is applicable in all three of our cases; however, as pointed out in one case (Case 1), the possibility of a supernormal phase in the area of bundle branch block must be considered.

4. In cases of sinus rhythm without intraventricular block, an ectopic pacemaker located in the septum may give rise to premature beats with a normal QRS duration, imitating nodal premature beats.

5. In Case 1 there was, in addition, another unusual arrhythmia, namely, a bigeminal rhythm which was interpreted as due to the fact

that every second beat was a premature beat originating in the S-A node, or, alternatively, as an instance of alternation of S-A conduction.

We are indebted to Dr. L. N. Katz for his valuable advice in this study.

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THE EFFECT ON THE PLASMA VOLUME OF DEHYDRATION PRODUCED BY A LOW-SALT DIET AND AMMONIUM CHLORIDE

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It has been accepted[1, 2] that the plasma volume remains relatively constant with dehydration because it is protected by the much larger extracellular fluid volume. With the use of improved techniques, however, it has been found that the plasma volume is not constant, but shows considerable fluctuation. It has been demonstrated in animal experiments that the plasma, as well as the interstitial fluid, contributes to the water lost in dehydration induced by the removal of gastrointestinal secretions[3] or by the intraperitoneal injection of glucose.[4] In the early stages of diabetic acidosis,[5] the plasma volume decreases before significant dehydration develops. In cardiac edema, where there is a great excess of interstitial fluid, the plasma volume is not constant, but will show a considerable decrease after diuresis, even though edema persists.[6, 7]

The mechanism of the action of ammonium chloride has been well established as a result of carefully controlled balance studies on normal and abnormal subjects.[8] In general, these persons were on fixed diets, usually low in sodium chloride and limited in fluid intake. Considerable variation is noted in the diuretic effect of ammonium chloride on the normal subjects, as reported in the literature; this is due, in part, to the use of different doses of the drug and to variations in the duration of the observation period. The diuresis varied from none[8b] to 2.5 kilograms, or 3.6 per cent of the body weight.[8c] Little information is available concerning the change in plasma volume, even as judged by changes in concentration of serum proteins or hematocrit values.

Since ammonium chloride is a frequently used diuretic, it would appear helpful to know how much diuresis it produces in normal persons in order to evaluate the diuretic response of patients. The studies in the literature are not closely comparable to the usual hospital method of employing ammonium chloride as a diuretic because the subjects had been on a fixed regimen for some days before the administration of the drug.

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This work was supported by grants from the Board of Governors of the Horace H. Rackham School of Graduate Study and from The Upjohn Company.
Received for publication April 16, 1943.

TABLE I

THE PERCENTAGE CHANGE IN PLASMA VOLUME, HEMATOCRIT VALUE, SERUM PROTEIN CONCENTRATION, AND BODY WEIGHT AFTER THE CONTINUOUS ADMINISTRATION OF 9 GM. OF AMMONIUM CHLORIDE DAILY

SUBJECT	DAYS ON 9 GM. OF AMMONIUM CHLORIDE	PERCENTAGE CHANGE IN PLASMA VOLUME	PERCENTAGE CHANGE IN CONCENTRATION OF SERUM PROTEIN	PERCENTAGE CHANGE IN HEMATOCRIT VALUE	PERCENTAGE CHANGE IN TOTAL BLOOD VOLUME	PERCENTAGE CHANGE IN BODY WEIGHT	ACTUAL CHANGE IN PLASMA CARBON DIOXIDE COMBINING POWER IN VOLUME PER 100 C.C.
1	3	-10.8	----	0	-10.7	-6.1	-18.0
2	3	- 8.1	+ 7.3	+ 1.8	- 6.6	-4.7	-11.2
12	3	- 9.3	----	+ 2.8	- 5.0	-4.2	----
13	3	-13.8	----	+ 3.7	- 9.0	-2.4	----
3	4	-13.7	----	-10.5	-15.3	-5.8	- 8.0
4	4	-14.1	+ 5.3	+ 1.1	-13.3	-5.1	- 6.7
5	4	-31.0	+ 6.5	+18.5	-19.3	-7.6	----
6	4	-12.5	+11.2	- 3.6	-12.4	-3.3	0
14	4	-20.0	----	+ 3.3	-11.8	-4.9	----
15	4	- 4.2	- 8.0	+ 2.2	- 2.5	-0.1	----
Average 3-4		-13.75	+ 6.5	+ 1.9	-10.6	-4.4	----
7	6	-24.4	+27.6	- 7.4	-25.1	-4.4	----
8	6	----	+15.7	----	----	-2.9	----
9	6	- 4.9	+ 7.5	----	- 5.6	-2.8	-12.2
10	6	- 6.8	+14.2	- 6.7	-11.7	-2.6	- 0.2
11	7	-23.0	----	0	-16.0	-1.3	- 1.0
5	8	-18.6	- 3.7	+15.5	- 7.2	-9.3	----
6	9	- 7.1	- 1.9	- 8.1	- 9.1	-3.5	- 4.0
9	10	+ 4.9	+ 6.2	+ 3.0	+ 5.6	-3.5	-21.8
10	10	+ 0.6	+ 2.9	- 8.7	- 6.7	-3.0	-23.6
8	13	- 4.4	+ 6.1	- 7.9	- 9.2	-3.6	----
11	15	-16.7	----	- 7.0	-15.2	-1.8	-19.0
6	16	-14.3	+ 1.8	- 7.0	-16.3	-3.6	- 1.0
9	16	-11.6	+10.0	+ 3.0	-11.1	-5.1	-25.4
10	16	- 1.3	0	- 4.1	- 4.9	-3.6	-19.8
8	19	- 2.3	+ 8.4	- 9.8	- 8.3	-4.3	----

In an effort to evaluate the response of normal subjects to a low-salt diet and ammonium chloride, and to further study the effects of dehydration on the plasma volume, the following observations were made.

METHODS

Fifteen hospital patients without evidence of cardiovascular or renal disease, who had never had edema and who were not ill at the time of the observations, were selected as normal subjects for study. Each patient had been on the routine hospital diet for several days before the observations were started. The subject was carefully weighed on a beam balance, accurate to 2 grams, in the postabsorptive state, on the morning of the observations. After the weighing he was placed on a comfortable stretcher and blood samples were taken for the determination of the plasma volume,[9] hematocrit value, serum proteins,[10] and, in some cases, CO_2 combining power.[11] After the initial observations were made, the subject was kept at rest in bed on a diet low in salt (about 2.5 Gm.), with 70 Gm. of protein, and the caloric content of the diet was adjusted to 40 per cent above the estimated basal caloric consumption. Fluids were permitted ad libitum. As far as could be ascertained, the diet was consumed completely, so that it can be assumed that changes in weight closely reflected changes in the water content of the body. At the start of this diet, 3 Gm. of ammonium chloride in 0.5 Gm., enteric-coated tablets were taken with each meal, so that 9 Gm. of ammonium chloride were ingested daily.

In the postabsorptive, rested state, the plasma volume of the normal subject is remarkably constant. In this laboratory the estimation of plasma volume was repeated fourteen times on successive mornings on twelve normal subjects in the rested, postabsorptive state, and showed an average variation of plus 0.88 per cent; the greatest variations, in one instance each, were plus 6 and minus 5 per cent. These results are in accord with those of others.[12, 13]

RESULTS

The observations on the majority of the subjects were completed after three or four days on ammonium chloride, chiefly because either they were no longer available for study or an adequate diuresis was produced. The alterations in total blood volume, plasma volume, hematocrit value, serum protein, and weight, expressed as percentage change from the initial determinations, are given in Table I. Plasma volume varies considerably with the size of the body, so that changes in the plasma volume of a group of persons of different size cannot be directly compared.

Ten subjects who received the drug for three or four days experienced an average diuresis of 4.4 per cent of their body weight, with a fall in plasma volume of 13.8 per cent. The hematocrit and serum protein values increased, although these changes were considerably less than the change in plasma volume, and failed to reflect accurately the fall in plasma volume. The actual change in plasma volume in these people averaged 436 c.c., with an average weight loss of 3 kilograms. The decrease in plasma volume accounted for 12.2 ± 1.2 per cent of the

total weight lost. The greatest change was noticed in Case 5, i.e., a decrease in plasma volume of 1,120 c.c. and a 4.6 kilogram weight loss.

Six subjects who received ammonium chloride for six to eight days showed a considerably greater variation in response which was in part the result of the selection of the cases. Some subjects who did not show an adequate diuresis after three or four days were allowed to continue the drug for a longer period before the observations were repeated.

Subsequent observations after nine to nineteen days on ammonium chloride indicated that the plasma volume was in part restored after its initial fall, in spite of the continued loss of water from the body as judged by the progressive weight loss. These fluctuations in the plasma volume are recorded in Table II.

TABLE II

THE PERCENTAGE CHANGE IN PLASMA VOLUME, HEMATOCRIT VALUE, SERUM PROTEIN CONCENTRATION, AND BODY WEIGHT AFTER THE CONTINUOUS ADMINISTRATION OF 9 GM. OF AMMONIUM CHLORIDE DAILY

SUBJECT	DAYS ON 9 GM. OF AMMONIUM CHLORIDE	PERCENTAGE CHANGE IN PLASMA VOLUME	PERCENTAGE CHANGE IN CONCENTRATION OF SERUM PROTEIN	PERCENTAGE CHANGE IN HEMATOCRIT VALUE	PERCENTAGE CHANGE IN BODY WEIGHT
5	4	-31.0	+ 6.5	+18.5	-7.6
	8	-18.6	- 3.7	+15.5	-9.3
6	4	-12.5	+11.2	- 3.6	-3.3
	9	- 7.1	- 1.9	- 7.1	-3.5
	16	-14.3	+ 1.8	- 7.0	-3.6
8	6	----	+15.7	----	-2.9
	13	- 4.4	+ 6.1	- 7.9	-3.6
	19	- 2.3	+ 8.4	- 9.8	-4.3
9	6	- 4.9	+ 7.5	----	-2.8
	10	+ 4.9	+ 6.2	+ 3.0	-3.5
	16	-11.6	+10.0	+ 3.0	-5.1
10	6	- 6.8	+14.2	- 6.7	-2.6
	10	+ 0.6	+ 2.9	- 8.7	-3.0
	16	- 1.3	0	- 4.1	-3.6
11	7	-23.1	----	0	-1.3
	15	-16.7	----	- 7.0	-1.8

Of considerable interest was the actual weight lost by these patients who had no suggestion of edema. The average weight loss of the group of fifteen subjects after receiving the diet and ammonium chloride for three to seven days was 2.47 kilograms. Continuation of the drug over a longer period was associated with a continued loss of weight, although the changes were quite small.

DISCUSSION

It is apparent from the results of these studies that the plasma volume shares in the dehydration induced by ammonium chloride. It is, of course, true that the majority of the water lost was derived from the reservoirs other than the plasma volume, but in certain instances there was a profound reduction of plasma volume.

Since sodium and potassium balance studies were not carried out on these subjects, it is not known whether the majority of the water lost under these circumstances came from the interstitial fluid or from the cells. However, others[8] have found that both sodium and potassium are lost in the urine, which suggests that the lost water must come from both the extracellular and intracellular fluid compartments. Gamble indicated that at first the water loss comes largely from the extracellular fluid and later the intracellular fluid.

The fluctuations in plasma volume after the initial fall continued in spite of progressive loss of body water. In general, these subsequent changes were toward a restoration of the plasma volume, and suggest that considerable shifts of water must occur within the body as diuresis continues, presumably because of removal of water from the cells or from extracellular fluid that is not readily mobilized. Judging from the observations of others,[3, 4, 8] who have found that a considerable amount of potassium is lost in the urine, it would appear that the plasma volume was made up by shift of water from the cells.

There was only a directional relationship in these cases between the intensity of the diuresis and the fall in plasma volume. Some cases, in which the diuresis was large with a relatively small decrease in the plasma volume, would suggest that the plasma volume was well protected by the extracellular fluid. In others, however, the large decrease in plasma volume with little change in weight suggested that there was very little protection of the plasma volume. As far as we could ascertain, all subjects were well hydrated and had been on the same hospital regimen for several days before the observations were made.

The diuresis experienced by some of these subjects was greater than that reported in the literature. These observations, however, represent the response of "normal" subjects who had been on the usual hospital regimen, with salt and water ad libitum, to the low-salt diet, as well as to large doses of ammonium chloride, over a three- to seven-day period. In general, in the cases previously reported,[8] the subjects were on a diet limited in salt and fixed in its constituents for some days before the administration of the drug. Loeb, et al.,[8e] however, noted no difference in the loss of potassium, sodium, magnesium, or calcium with the administration of ammonium chloride in the case of their carefully studied normal subject when he was on a "salt poor" diet and on the same diet with an additional 120 milliequivalents of sodium chloride.

These results suggest that it is not uncommon for a normal, hospitalized patient to have a diuresis of 2 to 4 kilograms on a low-salt diet and 9 Gm. of ammonium chloride per day. Such a diuresis in patients suspected of having edema has often been incorrectly interpreted as evidence of edema, but it represents only the response of a normally hydrated person to the diuretic regimen.

A comparison between the percentage change in plasma volume and the percentage change in hematocrit values and the concentration of

serum proteins shows a considerable discrepancy. Certainly, the changes in hematocrit values completely failed to express the changes in the plasma volume. This can in part be explained by the fact that determinations of the plasma volume require from 50 to 80 c.c. of blood, and, therefore, the loss of erythrocytes which may be expected from repeated determinations would produce a lower hematocrit value. It does not adequately explain the changes noted with the second plasma volume determination, for it seems unlikely that the removal of only 50 c.c. of blood three or four days previously would suffice to produce this loss of erythrocytes. The inability to accurately measure changes in plasma volume by changes in the hematocrit value has been demonstrated before by Ebert and Stead.[14, 15] They have indicated that shifts of blood from the larger to the smaller vessels may produce such changes in the hematocrit value without alterations in the number of erythrocytes in the circulation.

The changes in the concentration of serum proteins were consistently less than the changes in plasma volume, although in the same direction. As with the hematocrit, the changes in the concentration of serum proteins failed to express the extent of the dehydration of the plasma. This has been noted by others,[3, 16, 17] and suggests that a change in the concentration of serum proteins as an index of the change in plasma volume is not reliable. A change in the concentration of serum proteins may indicate only a directional shift in the plasma volume, but not a quantitative change, for the change in plasma volume is generally greater than the change in serum protein concentration. The failure of the serum proteins to follow more closely the changes in plasma volume is in accord with the concept of Madden and Whipple[18] that the serum protein is in a state of "dynamic equilibrium." It suggests that a decrease in the volume of the plasma induced over several days may be associated with decreases in the total amount of protein in the plasma.

CONCLUSIONS

1. Dehydration induced in man by the use of a low-salt diet and 9 Gm. of ammonium chloride daily is associated with a decrease in the plasma volume and a smaller rise in serum proteins and hematocrit values.

2. The amount of water loss varied considerably, but, in general, amounted to 3 or 4 per cent of body weight.

3. Only a directional relationship existed between the decrease in the plasma volume and the amount of diuresis.

4. The difference in the concentration of serum proteins or hematocrit values failed to reflect quantitatively the changes in the plasma volume.

5. Continued administration of ammonium chloride was accompanied by a secondary rise in plasma volume toward the control level, with subsequent fluctuations, although diuresis persisted.

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THE CIRCULATION IN MAN IN CERTAIN POSTURES BEFORE AND AFTER EXTENSIVE SYMPATHECTOMY FOR ESSENTIAL HYPERTENSION

I. Physiologic Aspects*

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The effect of posture on the circulation has long been a subject of interest to many students of vascular physiology. This subject has assumed increasing significance since the syndromes of spontaneous and of postoperative orthostatic hypotension have been recognized clinically. The relatively recent introduction of extensive sympathectomy for the relief of essential hypertension has resulted in opportunities for seeing and studying certain persons who have orthostatic hypotension and orthostatic tachycardia after this type of operation. Thus, information relative to the dynamics of the circulation which formerly had to come solely from studies on animals can now be obtained from studies on man.

HISTORICAL REVIEW

A good résumé of the historical aspects of the operation of sympathectomy for hypertension may be found in an article by Adson, Craig, and Brown.[1] Roth made perhaps the first extensive study of the effects of posture on the blood pressure and pulse rate after sympathectomy. She noted that no significant orthostatic decreases in blood pressure were produced by operations which did not produce extensive abdominal sympathetic denervation.

Allen and Adson[2, 3] have reported on the physiologic effects of extensive sympathectomy[1] on essential hypertension. More recently, Adams and his co-workers[4] studied the effects of extensive sympathectomy on the cardiorenal system. They found that the pulse rate and cardiac output were reduced after sympathectomy.

PURPOSE, SCOPE OF STUDY, AND DEFINITIONS

The purpose of the present investigation was to study, by as many approaches as were practicable under controlled conditions, the physiologic effects of sympathectomy and its effect with change of body

Received for publication May 3, 1943.

*Abridgement of a portion of thesis submitted by Dr. Gambill to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Medicine.

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posture. Accordingly, we studied the effect of the horizontal and the 60-degree head-up postures on (1) pulse rate, (2) blood pressure, (3) pulse pressure, (4) differential blood pressure, (5) response to the Flack test, and (6) cardiac output before and after extensive sympathectomy in ten cases of essential hypertension (Cases 1 to 10 of this and the succeeding report). In addition, the circulation time and the response to the cold-pressor test were studied while the patients were in the 60-degree head-up posture, and the volume of the leg while they were standing erect. Further studies were done on the same persons in an effort to modify orthostatic vascular responses; these studies will be reported in a subsequent paper. The word "orthostatic" is used in this report to refer to the 60-degree head-up posture, as well as to the erect or standing posture, although, strictly speaking, the term refers to the latter only.

It was deemed more advisable as well as more practicable to study a small number of cases from many aspects rather than a larger number less thoroughly and extensively. We realize the hazards of attempting to interpret percentages based on such small groups of cases. This becomes all the more obvious when the marked lability of the various factors which comprise the total picture of the circulation, particularly in cases of hypertension, is recalled.

Experience has shown that, in the early days of convalescence after extensive splanchnic sympathectomy for hypertension, the average patient cannot tolerate the upright posture long without syncope. The 60-degree head-up posture, therefore, was selected for most of the studies which were made, since it was felt that most patients could tolerate this posture. We are fully aware that use of the 90-degree head-up posture would have given a more accurate picture of the total effect of gravity on the circulation. We believe, however, that the differences in circulatory reaction which occur between the 60- and 90-degree head-up postures are largely quantitative. The 90-degree, or erect, posture has its disadvantages also. for certain muscular movements and muscular tension would be superimposed, which would make it more difficult to evaluate the role of gravity. We were more interested in knowing the trend of reactions.

PATIENTS STUDIED AND PROCEDURE

Seven of the patients were men and three were women. Their ages ranged from 25 to 57 years; the average age was 39.6 years. Seven patients had hypertension, Group 2, and three, hypertension, Group 3, according to the classification of essential hypertension by Keith, Wagener, and Barker.[5] All underwent bilateral, subdiaphragmatic, retroperitoneal, intra-abdominal resection of the splanchnic nerves, celiac ganglia, and upper two lumbar sympathetic ganglia and intervening trunks. In addition, the ninth, tenth, and eleventh thoracic sympathetic ganglia and intervening trunks were resected in two of the cases. Preoperative studies were made about four days after the patients were admitted to the hospital. Postoperative studies were done, on the average, twelve days after the second stage of sympathectomy. The patients had been walking for about five days prior to the postoperative studies.

All determinations except cardiac output were made at one session in an air-conditioned room in which the relative humidity was 40 per cent and the temperature ranged from 78 to 82° F. Studies of cardiac

output were made on the next day. A tilt table was used which permitted observations while the patients lay on the table in the horizontal and in the 60-degree head-up postures. Ordinary blood pressure cuffs were used on one arm and on both thighs just above the knees. The cuffs on the thighs were reinforced by towels fastened snugly with pins. For measurements of blood pressure in the thighs, Tycos aneroid sphygmomanometers which had been checked for accuracy against a mercury manometer were used. The cuffs were 12 cm. in width. Judging from studies by Wiggers,[6] a cuff that wide should give fairly accurate readings. A Bowles stethoscope was used, and the diastolic pressure was noted at the level at which auscultatory sounds were suddenly muffled. Patients rested on the table for at least twenty minutes before any studies were begun. In general, three determinations of blood pressure and pulse rate were made at intervals of two minutes in each of the two body postures.

PULSE RATE

The pulse rates of all patients in the horizontal posture were higher after operation than before operation; the average postoperative increase was 13 beats per minute. The pulse rate while the patients were in the 60-degree head-up posture averaged 21 beats more after sympathectomy. The rate of acceleration of the pulse was studied by counting the pulse at intervals of fifteen, thirty, sixty, and 120 seconds after the patient was moved to the 60-degree head-up posture. After this, the patient was returned to the horizontal posture and the pulse rate was again counted after fifteen seconds. The results are shown in Fig. 1. Thus, the pulse rate was not only higher, but had a tendency to accelerate continuously after operation, in contrast to the tendency preoperatively to attain a fairly constant level after the patient had been in the head-up posture for thirty seconds.

Roth[7] noted in a study of twelve cases of essential hypertension that active assumption of the erect posture, which is not entirely comparable with this study, resulted in an average increase of 12 beats per minute prior to sympathectomy and an average increase of 32.9 beats per minute subsequent to sympathectomy. Adams and his co-workers, on the contrary, found a slight decrease in heart rate when subjects were in the horizontal posture after sympathectomy.

The exact reason for the invariably faster pulse rate in both postures which was found in our series of cases after sympathectomy is not known. We doubt whether the Bainbridge reflex has much to do with it, for a tight abdominal binder, which should increase venous return to the right auricle and perhaps increase venous pressure within the right auricle (that is, activate the Bainbridge reflex), actually slows the heart. When patients are in the head-up posture after sympathectomy, the blood pressure may fall to rather low levels and evidences of impending syncope may appear. Reduction of pressure in the right auricle would be expected under these circumstances; yet, the pulse rate actually accelerated. It may be that, in such persons, vasomotor

reflexes which originate from pressure changes within the thoracic aorta and within the carotid sinuses exert a greater role in the regulation of blood pressure and pulse rate than vasomotor reflexes which arise from pressure changes within the right auricle. The former reflexes, too, may be activated more readily than the latter. Such an arrangement seems not only reasonable but desirable for the organism, since it would afford a quicker and a more direct control of the circulation, particularly for such vital structures as the brain, by counteracting sudden or harmful decreases or increases in blood pressure.

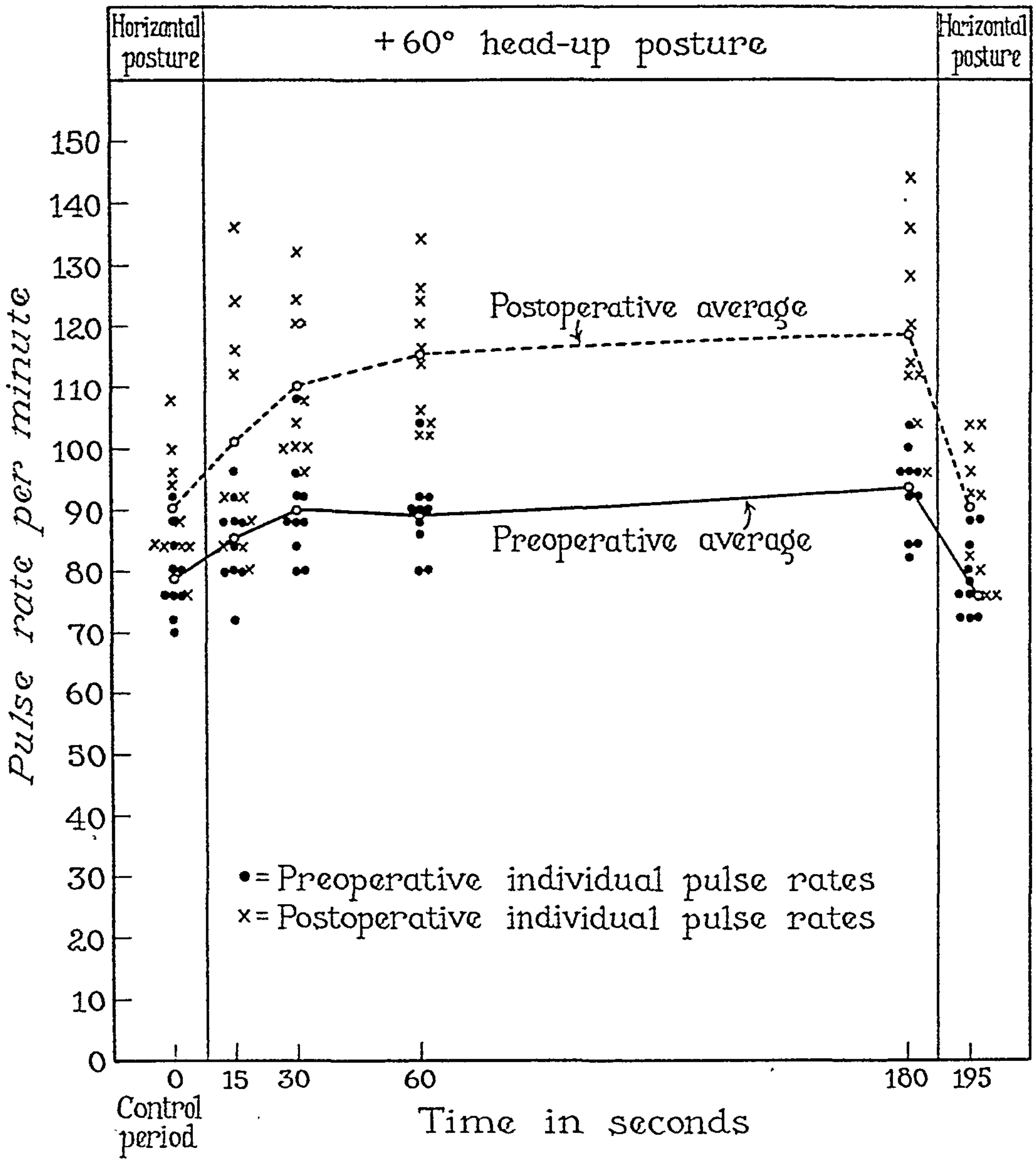

Fig. 1.—Preoperative and postoperative pulse rate in horizontal posture and at increasing time intervals after passive tilt to 60-degree head-up posture.

According to this concept, the increased pulse rate after sympathectomy could be due to a reduction in the number of pressoreceptive stimuli originating within the thoracic aorta and within the carotid sinuses as a result of a decrease in intra-aortic and intracarotid blood pressures secondary to a general decrease in peripheral resistance.

BLOOD PRESSURE

The consensus[8] as to the so-called normal response of the blood pressure when subjects are moved from the horizontal to the erect posture is that the systolic pressure does not change materially, whereas the diastolic pressure usually rises; many workers have reported a rise of 8 to 10 mm. of mercury in the diastolic pressure. In a recent study of 112 persons who had essentially normal blood pressure, one of us (Gambill[9]) found the systolic pressure unchanged, while the diastolic pressure rose an average of 6 mm. of mercury after subjects had stood for a period of three minutes.

The present study of blood pressure in the horizontal posture revealed that sympathectomy was followed by an average decrease of 21 mm. in systolic, and an increase of 7 mm. in diastolic, pressure. Study of the blood pressure in the 60-degree head-up posture before and after operation revealed that operation resulted in an average decrease of 36 mm. in the systolic, and 21 mm. in the diastolic, pressure (Fig. 2). When patients were moved on the tilt table from the horizontal to the head-up posture after operation, the systolic pressure decreased an average of twice as much, and the diastolic pressure, seven times as much, as before operation. Even in cases of marked orthostatic hypotension and tachycardia, vascular adjustments on return of the patient to the horizontal posture were rapid. For example, after one patient (Case 1) had been in the 40-degree head-up posture for seven minutes, the systolic pressure at the time of this study was 62, and the pulse rate was 132 per minute. Within twenty seconds after he was returned to the horizontal posture the systolic pressure was 116 and the pulse rate had decreased from 132 to 76.

Allen and Adson[3] stated that orthostatic hypotension and tachycardia definitely disappear a variable time after sympathectomy. The mechanism involved in the change is not known.

DIFFERENTIAL BLOOD PRESSURE

By differential blood pressure is meant the difference in blood pressure between the thigh and the arm. Careful studies in recent years, particularly those of Strang,[10] Bazett,[11] Hamilton and co-workers,[12] Cady,[13] and one of us (Gambill[9]), leave little doubt that a difference exists in the blood pressure in the thigh and arm of persons with normal pressure. Cady studied the differential blood pressure in seventy-five cases of hypertension and in seventy-five cases of normal pressure. He found that extensive sympathectomy reduced the difference in blood pressure in the thigh and arm. His conclusion was that this difference in pressure is due to differences in peripheral resistance in the leg and arm, and that any procedure which tends to equalize the resistance in the arteries of the two limbs also tends to equalize the pressures within these vessels. Conversely, unequal variations in

the resistance of the arteries of the leg and arm would affect the differential pressure. Bazett[11] postulated that the difference in blood pressure in the leg and arm was due to the greater transmission of kinetic energy into pressure energy in the leg than in the arm.

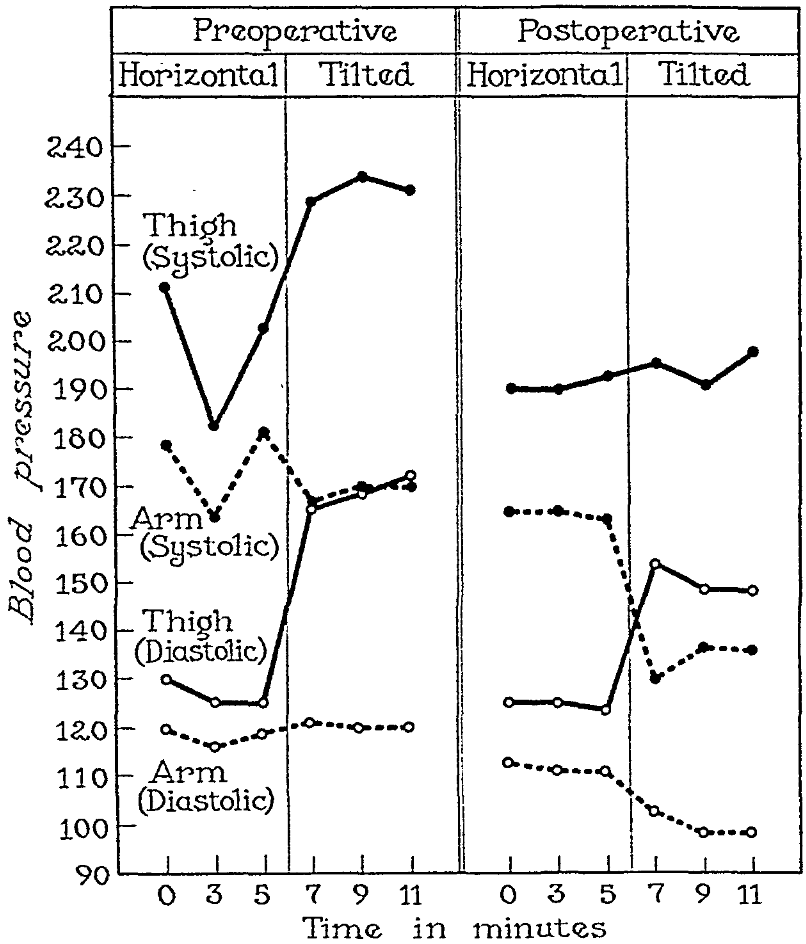

Fig. 2.—Mean blood pressures in arm and thigh in ten cases in horizontal and tilted (60-degree head-up) postures before and after sympathectomy.

The differential blood pressure in the present investigations was calculated from measurements of blood pressure from the arm and leg according to the procedure outlined. Contrary to expectations, sympathectomy actually resulted in an average increase of 8 mm. in both the systolic and diastolic differential pressures when the patients were in the horizontal posture. In the head-up posture after sympathectomy, reductions in systolic pressure were the same in the arm and leg, but reductions in the diastolic pressures were slightly greater in the leg. A greater reduction of blood pressure might be expected in the leg than in the arm if only the theoretical effect of sympathectomy on the reactivity of the vessels in the sympathectomized limb were considered. Such a result does not necessarily occur because peripheral resistance is only one of several elements which determine the level of blood pressure; cardiac output and circulating blood volume are among other factors which also may affect it. The fact that the diastolic blood pressure in the arm decreased after sympathectomy when patients were

placed in the head-up posture stresses the role of factors other than local vascular reactivity in determining blood pressure levels, for the arm vessels were not sympathectomized.

PULSE PRESSURE

Schneider and Truesdell,[14] after studying the postural reactions of a large number of healthy persons, concluded that the product of pulse rate and pulse pressure was unchanged with change of posture. It has been stated[15] that a pulse pressure of less than 30 or more than 50 mm. Hg is abnormal. Sewall[16] concluded, after a study of several hundred persons, that the pulse pressure always decreases when a change is made from the recumbent to the erect body posture. This decrease usually is the result of the decline in systolic and the rise in diastolic pressure which occurs on assumption of the upright posture.

The purpose of the present study was to observe what effect sympathectomy has on pulse pressures in the arm and leg when the patients were in the horizontal and in the 60-degree head-up postures.

The average pulse pressure in the arm when the patients were in the horizontal posture decreased 16 mm., and that in the leg decreased 12 mm., after sympathectomy. After sympathectomy, when the patients had remained for one minute in the 60-degree head-up posture, the average decrease in pulse pressure was 21 mm. in the arm and 24 mm. in the leg. The greatest decrease in pulse pressure after operation occurred in those cases in which hypotension was greatest in the head-up posture (Fig. 3). Although both systolic and diastolic pressures decreased when patients were placed in the head-up posture after operation, the lowered pulse pressure was predominantly the result of a greater decrease in the systolic than in the diastolic pressure.

Response to Flack Test.—The work of Grimes[17] and MacLean and Allen[18] has emphasized the possible significance of the Flack test in physiology and in clinical medicine. As a result of a study of 1,000 subjects in twenty years, Grimes considered a systolic rebound of 25 mm. Hg or less as a normal response to this test, and a rebound of more than 25 mm. Hg as an abnormal response.

It was felt that a study of the influence of certain postures on the Flack test before and after extensive sympathectomy might throw some light on the role of venous return to the heart in the regulation of the circulation, particularly since considerable orthostatic hypotension is likely to develop after sympathectomy. The test as used in the present study was as follows: The patient blew against the column of mercury in the sphygmomanometer until it attained a height of 20 mm., and maintained it at that level for twenty seconds. The blood pressure in the arm was measured during the last ten seconds of this period, after which the pressure within the arm cuff was quickly raised to a point higher than the previous control systolic level. After cessation

of blowing, the cuff was deflated rapidly until the first systolic sound was heard. This sound was designated as the level of the rebound pressure. In most instances the test was performed twice, and the average of the two rebound pressures was calculated. This test was done while patients were in the horizontal posture and again after they had been in the 60-degree head-up posture for two minutes. The term "rebound" denotes the number of millimeters of increase or decrease, respectively, in the systolic blood pressure above or below the level of the control blood pressure.

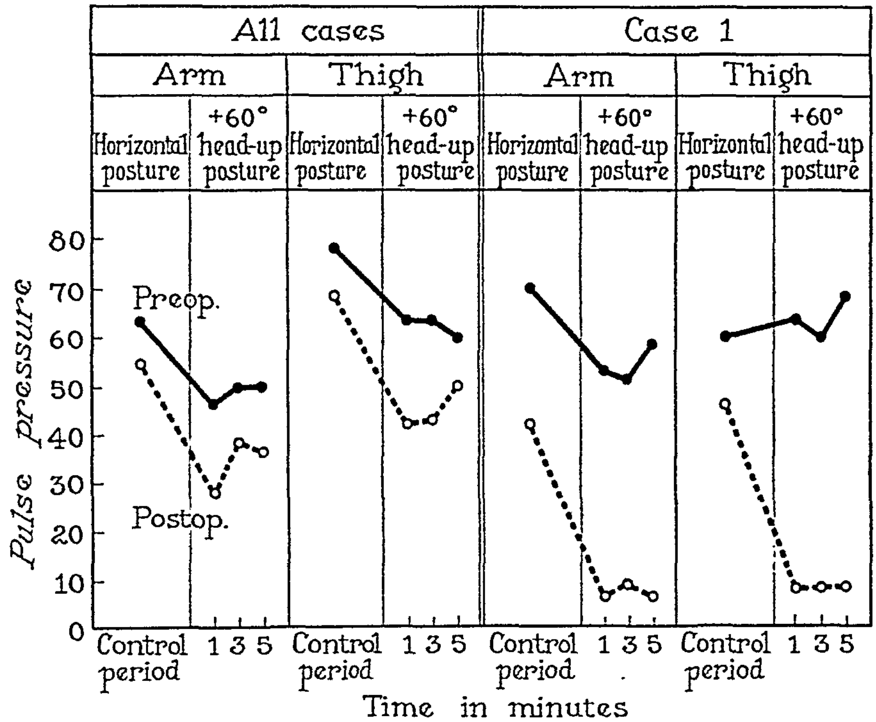

Fig. 3.—Comparison of average pulse pressures in arm and thigh in all ten cases with those in Case 1. Severe orthostatic hypotension and tachycardia developed in Case 1 after operation.

Prior to operation, the Flack test resulted in a decrease in systolic blood pressure in both postures; the greatest decrease occurred when patients were in the head-up posture. The diastolic pressure during the Flack test increased when the patients were in the horizontal posture but decreased when they were in the head-up posture. The systolic rebound pressure averaged 15 mm. more when the patients were in the horizontal posture than when they were in the head-up posture. After sympathectomy, when the patients were recumbent, the test resulted in eight times more reduction in systolic blood pressure than before operation. Whereas the diastolic pressure increased an average of 46 mm. during the Flack test in the horizontal posture before operation, it decreased in every instance when the test was similarly performed after operation. The systolic rebound pressure when the patient was in the horizontal posture was only two-thirds as great after as before operation. After operation, the response to the Flack test in

the head-up posture was strikingly impaired. In fact, the blood pressure during the period of blowing fell so low as to be obtainable in only three of nine cases studied. Whereas before operation the systolic rebound pressure in the head-up posture was 25 mm. more than the control value, after sympathectomy it was only 9 mm. more than the control pressure (Fig. 4). As expected, the lowest systolic rebound pressure occurred among patients who exhibited postoperative orthostatic hypotension and tachycardia. For example, in Case 1, as mentioned previously, orthostatic hypotension and tachycardia developed after sympathectomy, and, during the Flack test, syncope and a short convulsive seizure developed. One or two other patients had mild syncope during the Flack test.

It seemed desirable to see whether α-N-dimethyl-*p*-hydroxyphenethylamine sulfate (paredrinol sulfate) would improve the reactions to the Flack test. Accordingly, 20 mg. of this drug were given subcutaneously, and then the response to the Flack test was noted while the patient was in the horizontal posture. This was tried in Case 8 fifteen days after the second stage of sympathectomy and after control values for the Flack test had been ascertained. Only a slight improvement was noted in the response to this test after the administration of paredrinol sulfate. This patient had been walking around for a few days prior to the test, and had probably recovered a considerable degree of reactivity in the sympathectomized vessels—enough perhaps to counteract the effects of an increase of 20 mm. Hg in intrathoracic pressure while in the horizontal posture.

The exactness of the information revealed by the Flack test may be open to question, but the changes are so striking that their significance cannot be doubted. It is not assumed that the rebound pressures, as obtained, are absolutely accurate, for it is possible that the blood pressure may not have been obtained at its highest point. The fact that the pressure rebounded to the levels mentioned seems important.

Grimes felt that, other things being constant, the height of the rebound blood pressure varies inversely as the elasticity of the arteries. The general decrease in rebound pressure after sympathectomy in the present studies agrees with this view, for sympathectomized vessels have lessened constrictor tone, which makes them more distensible and reduces their elastic recoil. It has been stated that the pressure within a vein results (1) from the residuum of pressure created by cardiac systole, (2) from the degree of tonus in the vessels, which, in turn, is influenced by the vasomotor nervous system, and (3) from hydrostatic pressure. To these influences must be added the influence of muscular action with its milking effect on the veins. It is easy to reason, then, that sympathectomy, by decreasing the effect of at least the second and fourth factors, might decrease the venous pressure gradient from legs and abdomen to the thorax. Cardiac filling, there-

fore, could be impaired by relatively smaller increases in intrathoracic pressure. In fact, MacLean and Allen have shown by roentgenologic means that there is a decrease in the size of the heart shadow in cases in which the Flack test results in much hypotension. When cardiac filling is sufficiently impaired by such a procedure, even an accelerated pulse rate and localized increases in peripheral vasoconstriction might not prevent a decrease in blood pressure. If, in addition, hydrostatic forces are brought into play by tilting the subject to the semierect

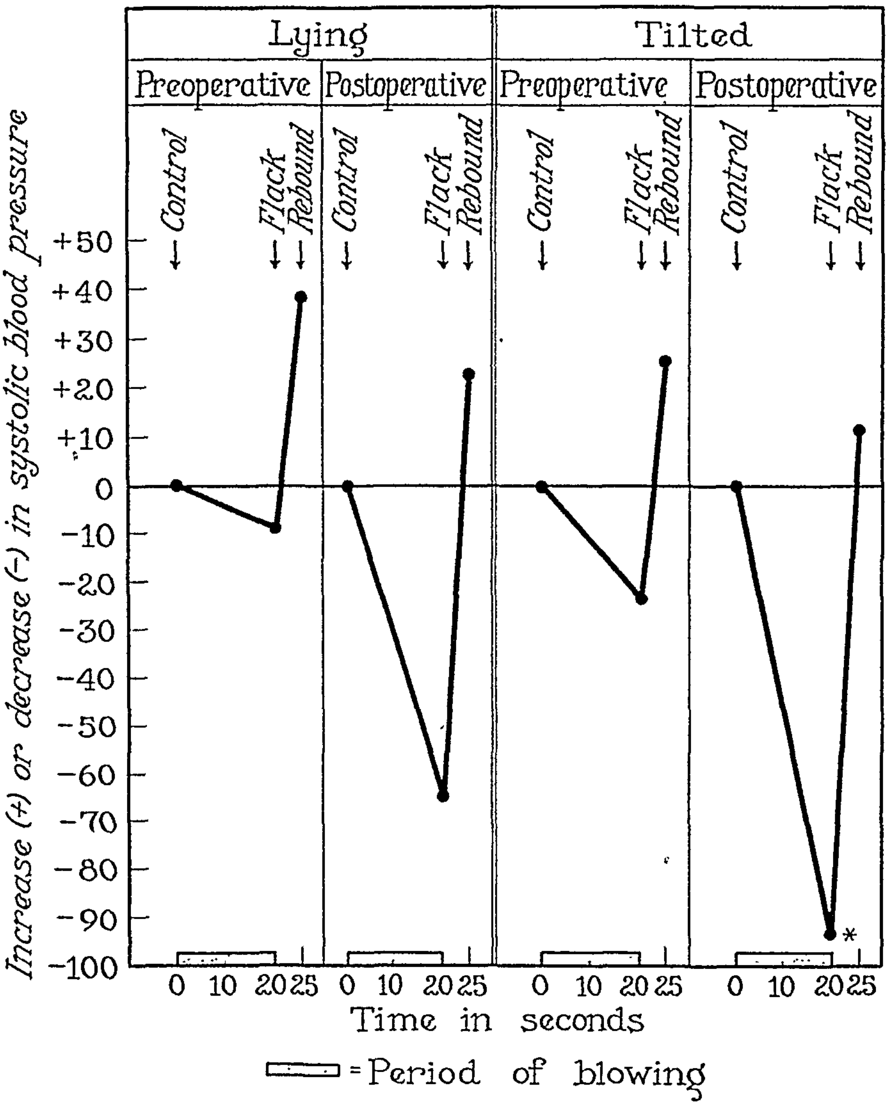

Fig. 4.—Flack test. Effect on systolic blood pressure of maintaining a column of mercury at 20 mm. for twenty seconds by blowing against it. The figure 94, as given for the depression in systolic pressure, may not be strictly accurate because it represents the average result for all cases, in some of which pressures were too low to measure. In these cases the decrease in pressure on blowing, for purposes of calculation, were taken as equal to the control systolic pressure. Almost certainly the pressure did not fall to zero.

posture, these effects are augmented. Thus, a greater decrease in the systolic blood pressure resulted during the Flack test while the patients were in the head-up posture than while they were in the horizontal posture. Sympathectomy seemed to augment these effects further. MacLean and Allen showed that a nearly normal Flack test resulted when subjects were lying in a 30-degree head-down posture.

CIRCULATION TIME

The circulation time from arm to foot and foot to arm was measured before and after sympathectomy. We were interested in comparing the circulation time in cases of postoperative orthostatic hypotension with that in cases in which this condition did not develop, in an effort to obtain additional information concerning the mechanism of this phenomenon. Recent studies of the circulation time of sympathectomized patients have been made by Kvale and associates[19] and Smith and associates.[20]

The circulation time from arm to tongue, arm to foot, foot to tongue, foot to arm was studied in seven of the ten cases while the patients were in the 60-degree head-up posture, under the environmental conditions mentioned previously. The subjects had been without food from four to seven hours prior to the test, and had been lying on the tilt table for at least an hour before the test was done. Macasol* was used as the test solution; 2 c.c. were used for the arm-to-foot time and 3 c.c., for the foot-to-arm time. This was given intravenously by means of a 3 c.c. syringe and a 20-gauge needle. The solution was injected into the median antecubital vein in order to ascertain the arm-to-foot time, and into one of the dorsal veins of the foot for the foot-to-arm time. Thirty seconds elapsed after release of the tourniquet before the test solution was injected in the punctured vein. A stop watch was employed for measuring the circulation time. Ten minutes elapsed between the injections in the arm and foot.

In three cases the circulation time increased, and, in four, it decreased after sympathectomy (Fig. 5). Whereas a decrease in the arm-to-foot and arm-to-tongue circulation time occurred after sympathectomy in the group in which the postoperative reduction in blood pressure was minimal to fair, the circulation time was more than doubled in the group in which the reduction in blood pressure was good and orthostatic hypotension developed after operation. Apparently, orthostatic hypotension is associated with a general slowing of the circulation. This may be related to marked vasoconstriction in the unsympathectomized upper part of the body and to a decrease in cardiac output when such subjects assume the head-up posture. The critical level of hypotension, below which circulation time is increased, has not been ascertained.

We tried to measure the circulation time from foot to tongue and from foot to arm without success, apparently because of pooling or stagnation of the test solution in the injected limb. This was suggested by the fact that no reaction was felt in the tongue for as long as three minutes after injection of the solution in the vein in the foot so long as the patient remained in the head-up posture. However, a

*Macasol is a mixture of magnesium sulfate, magnesium gluconate, calcium sulfate, sodium chloride, and copper sulfate in sterile distilled water, and is manufactured by Nepera Chemical, Inc., Yonkers, New York.

definite reaction occurred in the tongue, and then in the arm, about eight and sixteen seconds, respectively, after the patient was returned to the horizontal posture. Moreover, if, before returning the patient to the horizontal posture, a blood pressure cuff was placed around the thigh of the injected limb and was inflated above the diastolic blood pressure level, no reaction was experienced in the tongue for as long as three minutes after return of the patient to the horizontal posture. A strong reaction in the tongue and arm followed within six to ten seconds after deflation of the cuff. This and burning in the foot, relieved by assumption of the horizontal posture, offer additional proof that there was stagnation of the test solution in the leg while the patients were in the head-up posture. These observations indicate the difficulty of measuring circulation time in the head-up posture.

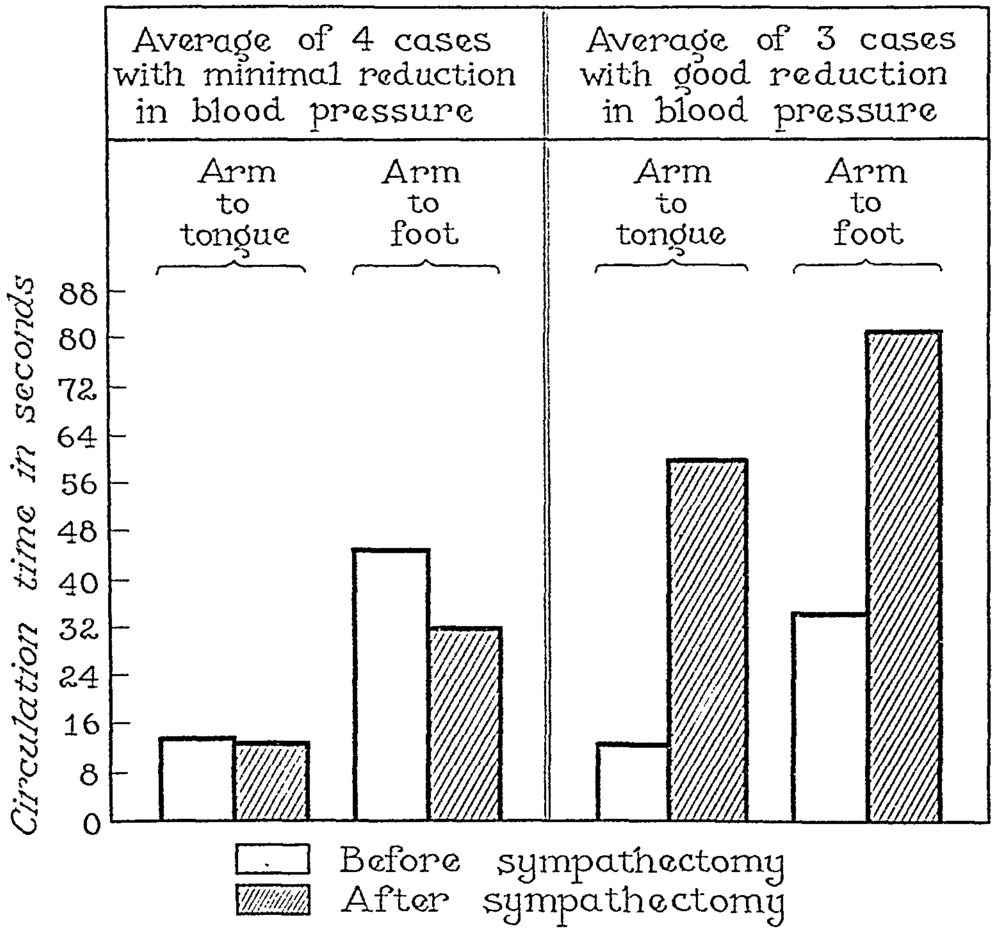

Fig. 5.—Average circulation time in seconds in 60-degree head-up posture before and after sympathectomy. Comparison of results obtained in four cases in which reduction of blood pressure was minimal with those in three cases in which reduction of blood pressure was good and considerable orthostatic hypotension and tachycardia followed sympathectomy.

RESPONSE TO COLD-PRESSOR TEST

Allen and Adson[2, 3] have observed that, in general, those patients who have good reductions in blood pressure as a result of sympathectomy tend to have the greatest diminution in blood pressure response to the cold-pressor test after sympathectomy, and vice versa.

The present study was done in an effort to learn more about the mechanism of the orthostatic hypotension which is so marked in some cases after sympathectomy. The test has been well established as a standard stimulus of blood pressure, and we felt that the results derived from it might also serve as a yardstick for comparison of the pressor effects of other agents which were employed during the investigations. The technique devised by one of us (Hines[21]) was used. The test was done while the patients were in the 60-degree head-up posture. They had been lying on a tilt table undergoing other studies for at least an hour before the test was done. They had been resting quietly on the table fifteen to twenty minutes prior to the test. Two minutes elapsed after the patient was placed in the head-up posture, and then a control blood pressure reading was taken, after which the test was performed.

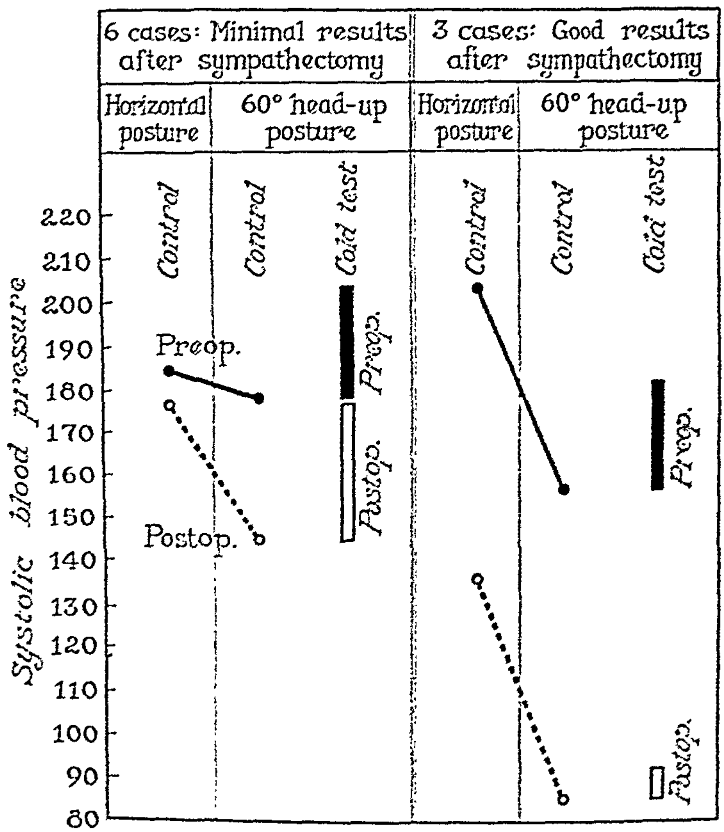

FIG. 6.—Effect of cold-pressor test with patients in 60-degree head-up posture. Comparison of cases in which reductions of blood pressure were minimal after sympathectomy versus cases in which reductions of blood pressure were good after sympathectomy.

As indicated in Fig. 6, in those cases in which the blood pressure was reduced considerably as a result of sympathectomy, the response to the cold-pressor test also was decreased by sympathectomy. On the other hand, patients who had little reduction in blood pressure postoperatively did not have a decreased response to the test. These results agree with those reported by Allen and Adson.[2, 3]

CARDIAC OUTPUT

All clinical evidence convinces the observer that marked degrees of orthostatic hypotension after sympathectomy must be associated with a reduction in cardiac output. The purpose of this study of cardiac output was to test that hypothesis. Certain investigators[22-24] have expressed the opinion that cardiac output changes little or not at all as a result of change in posture. However, most workers in this field[25-31] have noted significant decreases in cardiac output when the subjects stand erect. This was true of hypertensive, as well as normal, persons.

The cardiac output of five patients was measured in the horizontal and 60-degree head-up postures before and after sympathectomy. Two measurements were made on each patient in each position by the method described by Grollman. Basal metabolic rates were measured with the gasometer machine, using the open circuit method and the technique of Boothby and Sandiford.[32] Frequent determinations of blood pressure and pulse rate were made before and after each rebreathing test. Vital capacity was measured graphically by means of a spirometer.

The results are shown in Tables I and II. The variation between values obtained on the first and second tests were much greater for both postures after operation than they were before operation. The exact reasons for these differences are not clear, but we do not feel that they are related necessarily to technical error. It is more likely that they reflect the profound instability of the circulation which is obvious clinically so soon after sympathectomy. It would be interesting to repeat these observations several months after the operation, when the circulation has become readjusted and stabilized.

In four of the five cases, consumption of oxygen was decreased after sympathectomy. The basal metabolic rate was decreased in almost every instance after operation, and the average decrease was three times as much in the horizontal as in the head-up posture. The cardiac output was greater in both postures after sympathectomy; the greatest increase occurred when the patients were in the horizontal posture. Thus, in the horizontal posture, the cardiac output averaged 0.62 liter per square meter per minute more, and in the head-up posture 0.52 liter per square meter per minute more, after sympathectomy than it did before. However, a significant decrease in cardiac output occurred when the patients were moved from the horizontal to the head-up posture; the decrease averaged 0.56 liter per square meter per minute before operation and 0.66 liter per square meter per minute after operation. The stroke volume after operation was increased when the patients were in the horizontal posture, but was decreased after they were moved to the head-up posture. It was smaller in the head-up posture before, as well as after, the operation.

TABLE I

CARDIAC OUTPUT IN THE HORIZONTAL POSTURE

CASE	B.M.R. (PER CENT)	BLOOD PRESSURE (MM. HG)	PULSE RATE	O_2 CONSUMPTION (C.C. PER MIN.)	DIFFERENCE IN ARTERIAL AND VENOUS O_2 (C.C. PER L.) TEST 1	TEST 2	AVERAGE	CARDIAC OUTPUT (L. PER SQ. M. PER MIN.) TEST 1	TEST 2	AVERAGE	AVERAGE STROKE VOLUME (C.C. PER BEAT PER SQ. M.)
					Preoperative						
1	- 1	165/96 166/104	74- 72	141	82.9		82.9		1.70	1.70	23.6
2*	+11	176/118 178/120	76- 80	248	63.4	68.5	65.9	2.10	2.20	2.19	26.9
3	+ 8	186/110 182/116	84- 84	257	59.6	56.1	57.8	2.32	2.46	2.39	28.4
4	+ 5	160/124 160/120	96-100	199	58.2	65.2	61.7	2.26	2.02	2.14	21.8
11†	+32	166/110 192/122	86- 90	240	48.5	57.8	53.1	3.39	2.84	3.11	25.7
Mean	+11	170/112 176/116	83- 85	217	62.5	61.9	64.3	2.52	2.24	2.28	25.3
					Postoperative						
1	-16	126/ 88 124/ 92	72- 76	211	40.0	84.4	62.2	3.00	1.40	2.20	28.2
2	+ 2	140/ 98 156/108	84- 84	227	27.0		27.0	4.72		4.72	56.2
3	+ 6	178/118 184/116	86- 84	248	44.2	56.8	50.5	3.05	2.37	2.71	31.8
4	-11	144/112 146/114	88- 84	167	41.1	67.3	54.2	2.87	1.63	2.15	25.4
11†	0	166/116 184/116	80-100	175	54.5	40.1	47.3	2.29	3.12	2.70	33.7
Mean	-5.4	151/106 159/109	83- 86	206	41.4	62.1	48.2	3.15	2.12	2.90	35.1

*The patient was somewhat uncomfortable during the preoperative studies because of thoracic pain on the left side.

†Case 11 is not included in the series of ten cases mentioned at the beginning of this report. In this case, studies were limited to measurements of cardiac output.

Case 1 is very interesting. During the postoperative measurement of cardiac output with the patient in the head-up position, he was practically in syncope; the systolic pressure varied between 86 and 64 mm.; the diastolic auscultatory sounds were indistinct. The pulse rate during this time increased from 128 to 140 beats per minute; pallor was marked; the skin was cold and clammy, and the respirations were unusually deep and heavy, which may have had something to do with the high metabolic rate. The cardiac output decreased from an average of 2.2 in the horizontal posture to 1.09 liters per square meter per minute while he was in the 45-degree head-up posture. The stroke volume decreased from 28.2 c.c. in the horizontal, to 8.2 c.c. per beat in the head-up, posture.

Whether cardiac output can be measured accurately during such marked degrees of orthostatic hypotension as occurred in Case 1 is debatable. The acetylene method[24] for measuring cardiac output re-

TABLE II

CARDIAC OUTPUT IN 60-DEGREE HEAD-UP POSTURE

CASE	B.M.R. (PER CENT)	BLOOD PRESSURE (MM. HG)	PULSE RATE	O_2 CONSUMPTION (C.C. PER MIN.)	DIFFERENCE IN ARTERIAL AND VENOUS O_2 (C.C. PER L.) TEST 1	TEST 2	AVERAGE	CARDIAC OUTPUT (L. PER SQ. M. PER MIN.) TEST 1	TEST 2	AVERAGE	AVERAGE STROKE VOLUME (C.C. PER BEAT PER SQ. M.)
					Preoperative						
1	− 7	156/102 148/106	92- 92	153	101.5	88.8	95.1	1.51	1.72	1.61	17.5
2*	+27	160/134 180/120	96-100	293	58.8		58.8	1.83		1.83	18.7
3	+ 5	176/116 168/110	82- 92	252	79.7	68.6	74.1	1.70	1.97	1.83	21.3
4	+ 2	154/130 146/116	134-126	193	88.9	85.0	86.8	1.44	1.50	1.47	11.9
11	+18	150/104 160/106	84- 96	214	82.3	74.0	78.1	1.78	1.99	1.89	21.0
Mean	+ 9	159/117 160/112	98-101	221	82.2	79.1	78.6	1.65	1.80	1.73	18.1
					Postoperative						
1†	+27	86/ 70 64/ ?	128-140	252	143.0	114.5	128.7	0.99	1.20	1.09	8.2
2	+24	112/ 74 120/ 94	104-108	272	67.5	59.5	63.5	2.26	2.57	2.41	22.7
3	+ 2	154/100 156/110	96-100	240	91.7	41.5	66.6	1.42	3.45	2.28	22.8
4	−10	124/106 112/102	136-124	171	37.3	43.4	40.4	3.01	2.59	2.80	20.2
11‡	+ 5	144/110 138/106	108-116	183		49.6	49.6		2.64	2.64	23.6
Mean	+9.6	144/ 92 118/103	114-117	224	84.9	61.7	69.8	1.92	2.49	2.24	19.5

*This patient was somewhat uncomfortable during the preoperative studies because of thoracic pain on the left side.

†The 45-degree head-up posture was used after operation because syncope developed in the 60-degree head-up posture.

‡Case 11 is not included in the series of ten cases mentioned at the beginning of this report. In this case studies were limited to measurements of cardiac output.

quires an accurate measurement of the basal metabolic rate. It would seem that this would be difficult to obtain in instances like this, when the patient is breathing unusually heavily in an effort to improve the venous return to the heart and thus avoid syncope.

Boothby and Rynearson[26] have pointed out the essentially linear relationship between oxygen consumption and cardiac output. Harrison and Blalock[33] found in dogs that induced anoxia increased the cardiac output from 5 to 500 per cent. This, they stated, supports the hypothesis that capillary oxygen pressure is an important factor affecting circulatory minute volume. If this is true for the human being, it constitutes an important element to be considered when studies of cardiac output are done under conditions of marked circulatory stasis, such as

undoubtedly are associated with orthostatic hypotension after sympathectomy. The markedly slowed circulation time in such cases is probably associated with a certain degree of tissue anoxia which logically might affect the cardiac output. Boothby and Rynearson obtained somewhat variable results on successive measurements of cardiac output in a case of exophthalmic goiter, and suggested that this variation may represent the instability of circulation which is known to occur in such cases. We had similar experiences in the present investigation, particularly after sympathectomy. The conflicting results which have been obtained in studies of cardiac output by competent workers, using the same method, indicate the difficulties inherent in such studies.

VOLUME OF THE LEG

The purpose of this study was to note the effect of extensive sympathectomy on the volume of the leg when the patient was in the upright posture. In general, various workers[34-37] have observed that, in healthy persons, quiet standing results in increases in the volume of the leg. Turner and her co-workers[36] observed that this swelling was greater in summer than in winter. Most of the swelling appeared during the first minute of standing. Hallock and Evans[38] compared the swelling of the legs of normal persons with that of patients who had orthostatic hypotension and orthostatic tachycardia. They felt that filtration into the tissue spaces was increased in the latter group.

The volumes of the legs of four of the present series of patients, while they were standing, were estimated before and after operation. The patient inserted the leg rapidly into a steel pail especially constructed for this purpose and containing water, the temperature of which was between 86 and 95° F.; the water was essentially at the same temperature for any given patient before and after sympathectomy. The patients stood as quietly as possible for three minutes, during which time the amount of water which overflowed through the spout at the top of the pail was collected and measured. Each patient had been supine two to three hours prior to the test.

Under the conditions of this test, all four patients after sympathectomy exhibited an apparent reduction in the volume of the leg on standing, as indicated by the volume of water which was displaced (Table III). This decrease varied from 4.6 to 13.3 per cent of the total preoperative overflow value, or volume of the leg. The average reduction in volume was 7.3 per cent.

The method employed was rather crude, but it is felt that the degree and consistency of the changes are significant. The patients did not lose more than 8 to 11¼ pounds (3.6 to 5.1 kg.) between studies, which does not seem to explain fully the changes which were noted. Judging from our present knowledge of the circulation and because of the assumption that vasodilation is increased as a result of sympathectomy,

TABLE III

EFFECT OF SYMPATHECTOMY ON VOLUME OF THE LEG: CUBIC CENTIMETER WATER DISPLACEMENT, BEFORE AND AFTER SYMPATHECTOMY, ON STANDING IN A PAIL OF WATER FOR THREE MINUTES

CASE	TIME IN RELATION TO OPERATION	FASTING (HR.)	TEMPERATURE (° F.)			OVERFLOW IN 3 MIN.			WEIGHT OF PATIENT (LB.)
						TOTAL (C.C.)	LOSS		
			MOUTH	ROOM*	WATER		TOTAL (C.C.)	PER CENT	
5	Before	$4\frac{1}{2}$	98.6	82-80	95.0	3480			112
	22 da. p.o.	$3\frac{1}{2}$	98.0	80-78	95.0	3320	-160	- 4.6	?
6	Before	7	98.6	80	86.0	3320			115
	25 da. p.o.	7	99.6	80	86.5	2880	-440	-13.3	$103\frac{3}{4}$
7†	Before	$4\frac{1}{2}$	98.6	80	89.2	3835			125
	17 da. p.o.	16	98.0	81	89.2	3665	-170	- 4.8	117
8	Before	5	98.6	78	92.1	3520			118
	20 da. p.o.	5	99.0	81	92.1	3290	-230	- 6.5	109
Mean	Before	$5\frac{1}{4}$	98.6	80	90.6	3539			118
	21 da. p.o.	$7\frac{7}{8}$	98.6	80	90.7	3289	-250	- 7.3	110

*Humidity was 40 per cent before and after operation in all cases except Cases 7 and 8, in which the humidity after operation was not known.

†Patient was able to stand in a pail of water only one minute after operation because of impending syncope. At end of this period, there was only a slow dribble of about 100 drops per minute from the spout of the pail.

it would be logical to expect that the volume of the leg would be greater after sympathectomy. Why this failed to occur cannot be explained. One possible explanation might be that prolonged rest in bed incidental to the operation may have resulted in disengorgement or relative dehydration of the tissue spaces because of the decreased exposure of the legs to the influence of gravity.

COMMENT

No one knows why, as a result of the same operative procedure, orthostatic hypotension and tachycardia develop in certain cases and relatively little in others. The answer may lie in differences in constitutional make-up. It was interesting to observe that, in general, those patients who had the greatest postoperative orthostatic hypotension and tachycardia also had the greatest decreases in blood pressure and greatest increases in the pulse rate on being moved to the head-up posture before operation. For the sake of brevity, the table illustrating these observations was omitted from this paper. The number of cases studied is much too small to permit definite conclusions. Further observations along these lines seem desirable. It may be that the reaction of the blood vessels which is due to factors inherent in the vascular wall and the reaction which is due to external neurogenic influences acting on the vascular wall are present in different proportions in different persons. It may be that those patients who have marked degrees of orthostatic hypotension are the ones whose blood vessels are affected predominantly through external neurogenic influences. In such cases, sympathectomy would, perhaps, remove a relatively greater element of vasomotor control than when the intrinsic influences in the

vascular wall exert a predominant role. The fact that patients eventually recover[3] from the marked orthostatic hypotension indicates some compensating mechanism. No one knows what this mechanism is. It has been suggested[39, 40] that the sympathectomized vessels become sensitized to sympathin or epinephrine or similar humoral substances. The possibility of a certain degree of regeneration of the resected sympathetic nerves has not been excluded.[41]

SUMMARY AND CONCLUSIONS

Ten patients were studied in the horizontal and 60-degree head-up postures before and after extensive sympathectomy for essential hypertension. The important observations were as follows:

1. The pulse rate was definitely faster in every case and in both postures after sympathectomy.
2. When patients were changed from the horizontal to the 60-degree head-up posture, the systolic blood pressure fell twice as much, and the diastolic pressure fell seven times as much, after, as before, operation.
3. The difference in blood pressure between the leg and arm was little affected by sympathectomy. There was a slight tendency toward an increase in this difference after sympathectomy, which was contrary to what was expected.
4. Significant decreases in pulse pressure in the arm and leg followed sympathectomy. These decreases were greatest when the patients were in the head-up posture, and especially great among those who had postoperative orthostatic hypotension.
5. The performance of the Flack test was much impaired after sympathectomy. The greatest impairment occurred when the patients were in the head-up posture, and among those patients who had postoperative orthostatic hypotension. The systolic blood pressure during this test fell eight times as much, and the systolic rebound pressure was only two-thirds as great after operation as before operation.
6. The circulation time from arm to foot in the head-up posture decreased after operation in cases in which reductions in blood pressure were minimal to fair; it increased after operation in cases in which reductions in blood pressure were marked.
7. The circulation time from foot to arm was unobtainable in the head-up posture on the tilt table, apparently because of stagnation of the solution used for testing in the injected limbs.
8. Only those patients who had excellent reductions in blood pressure after sympathectomy had any real decrease in response to the cold-pressor test.
9. After sympathectomy the cardiac output was apparently greater in both postures. However, the cardiac output was less in the head-up posture than in the horizontal before, as well as after, sympathectomy. This difference was greater after operation, and was greatest in cases in which much postoperative orthostatic hypotension developed.

10. The stroke volume was increased in both postures after sympathectomy, but the stroke volume was always less when the patients were in the head-up posture.

11. The basal metabolic rate was decreased in both postures after sympathectomy. An actual increase in the basal metabolic rate apparently may occur while the patient is exhibiting a marked decrease in blood pressure in response to the head-up posture.

12. The volume of the leg on standing erect appeared to be decreased after sympathectomy in all cases studied; the average decrease was 7.3 per cent of the total preoperative volume. The exact reason for this unexpected observation has not been discovered.

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THE CIRCULATION IN MAN IN CERTAIN POSTURES BEFORE AND AFTER EXTENSIVE SYMPATHECTOMY FOR ESSENTIAL HYPERTENSION

II. Effect of Certain Mechanical Agents and Paredrinol on Blood Pressure and Pulse Rate*

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IN A PREVIOUS paper[1] we reported some of the physiologic effects on the circulation of extensive splanchnic sympathectomy and postural change in cases of essential hypertension. The studies to be reported in this paper were made on the same ten patients (Cases 1 to 10). In general, the same air-conditioned room and basic procedure, including the same dates of study, were employed in both instances.

This part of the investigation was concerned with modifications of blood pressure and pulse rate by (1) a tight abdominal binder, (2) bilaterally inflated cuffs around the thighs, (3) an abdominal binder plus cuffs around the thighs, (4) exercise of the legs, and (5) the administration of paredrinol sulfate. The blood-pressure-raising effects of some of these agents were compared to similar effects of the cold-pressor test. Controlled observations preceded each of the investigations. Each study was done before and after extensive sympathectomy, and, in most instances, while the patients were in the horizontal and in the 60-degree head-up postures.

TIGHT ABDOMINAL BINDER

The primary purpose of this portion of the study was to see whether such a binder would relieve the orthostatic hypotension and tachycardia which often follow extensive splanchnic denervation. The word "orthostatic" is used in this paper to denote any upright or partially upright position in which the head is higher than the feet. In most instances, this was the 60-degree head-up posture.

Various workers[2-9] have noted the beneficial effects of abdominal compression on the low blood pressure of certain persons and of animals under certain conditions when the upright posture is assumed. While studying vasomotor adaptation in animals, Hill, as early as

Received for publication May 3, 1943.

*Abridgement of a portion of thesis submitted by Dr. Gambill to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Medicine.

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TABLE I

EFFECT OF ABDOMINAL BINDER ON BLOOD PRESSURE (MM. HG.) AND PULSE RATE IN HORIZONTAL AND 60-DEGREE HEAD-UP TILTED POSTURES, BEFORE AND AFTER SYMPATHECTOMY*

CASE	PREOPERATIVE						POSTOPERATIVE						ORTHOSTATIC GAIN OR LOSS FROM BINDER	
	HORIZONTAL CONTROL		60-DEGREE HEAD-UP POSTURE				HORIZONTAL CONTROL		60-DEGREE HEAD-UP POSTURE					
			WITHOUT BINDER		WITH BINDER				WITHOUT BINDER		WITH BINDER			
	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE
1†							116/ 76	84	62/ 58	132	106/ 74	88	+44/+16	-44
2							166/ 90	84	128/ 76	100	126/ 86	104	- 2/+10	+ 4
3	220/140	88	200/130	92	206/140	96	178/120	88	164/112	100	150/108	108	-14/- 4	+ 8
4	164/120	80	146/120	96	160/120	98	150/116	88	138/100	128	116/100	112	-22/ 0	-16
5	160/100	68	164/108	88	164/110	84	184/112	96	160/110	118	182/126	114	+22/+16	- 4
6	194/124	72	198/136	90	214/140	80	194/140	104	180/138	128	204/144	128	+24/+ 6	0
7	168/114	88	154/118	112	162/134	104	160/130	108	100/ 96	152	114/104	140	+14/+ 8	-12
8	176/106	72	160/118	88	160/112	84	130/ 88	76	54/ 50	132	72/ 64	98	+18/+14	-34
9							190/130	100	164/124	108	166/128	124	+ 2/+ 4	+16
10							164/104	94	150/102	132	170/112	120	+20/+10	-12
Mean	180/117	78	170/122	94	178/126	91	163/111	92	130/ 97	123	141/105	114	+11/+ 8	- 9

*Blood pressures and pulse rates represent in almost every instance the third of a series of readings taken at two-minute intervals. The series of control readings in the horizontal posture were taken after approximately twenty minutes of rest on the table.

†After operation, patient could not tolerate the 60-degree head-up posture without syncope; hence a 40-degree head-up posture was used.

1895, found that abdominal compression prevented the syncope and death which resulted when animals were maintained in the vertical head-up posture, especially after chloroform poisoning or after splanchnicectomy. Such compression restored the blood pressure, which otherwise fell when the animal was in the head-up position. Adson and Brown[2] and Adson, Craig, and Brown[3] have noted the beneficial effects of a tight abdominal binder in counteracting the hypotension which occurs on assumption of the upright position after extensive sympathectomy.

In the present study, a many-tailed abdominal surgical binder was employed. Under the binder and over the abdomen were placed several folded towels which extended from the level of the lower ribs to the pubic region, so that, when the binder was tightened, pressure would be exerted posteriorly and upward as well as laterally against the abdomen. From two to four consecutive determinations of blood pressure and pulse rate were made at intervals of two minutes, first with the patients in the horizontal, and then in the 60-degree head-up, posture. The binder was then released, after which one or two determinations of blood pressure and pulse rate were made while the patient was still in the head-up posture. The patient was then returned to the horizontal posture. The results were compared to the control series of blood pressure and pulse rate readings which had been made in each position a few minutes previously. In some instances, the binder was tightened after its release while patients were in the head-up posture in order to note its effect under such circumstances. Six of the ten cases were studied before sympathectomy and all of the ten cases were studied after sympathectomy.

Results.—The results of this study are shown in Table I. Before operation, at the end of about five minutes in the head-up posture, the binder resulted in an average increase of 8 mm. Hg in the systolic, and 4 mm. in the diastolic, pressure, and an average decrease of 3 beats per minute in pulse rate. After operation the effect was an average increase in the systolic pressure of 11 mm., and, in the diastolic pressure, of 8 mm., and a decrease in the pulse rate of 9 beats per minute. The most striking benefit resulted when the binder was used in cases in which considerable orthostatic hypotension and tachycardia occurred, as in Case 1 (Fig. 1). In the 40-degree* head-up posture the systolic blood pressure at the end of the control period of three minutes was 62 mm., the diastolic, 58 mm., and the pulse rate, 132 beats per minute. At this time the patient was quite pale and cold and was virtually in syncope. By contrast, even at the end of seven minutes in this position, during which time the binder was tightly in place, the systolic pressure was 106, the diastolic pressure, 74, and the pulse rate, 88. The binder thus produced a net increase of 44 mm. Hg in systolic pressure and 16 mm. in

*This posture was used because more erect postures resulted in syncope.

diastolic pressure, and a decrease of 44 beats per minute in the pulse rate. The pulse pressure rose from 4 to 32 mm. as a result of using the binder.

In Case 8 the reduction in blood pressure was only fair as a result of the operation. Before operation, when this patient was in the head-up posture, the binder had little effect on the blood pressure and pulse rate. After operation, however, the binder resulted in a net increase of 18 mm. in systolic pressure and 14 mm. in diastolic pressure, and a decrease of 34 beats per minute in pulse rate. With these changes, much less pallor, clamminess of the skin, and faintness were noted, and the patient felt much stronger.

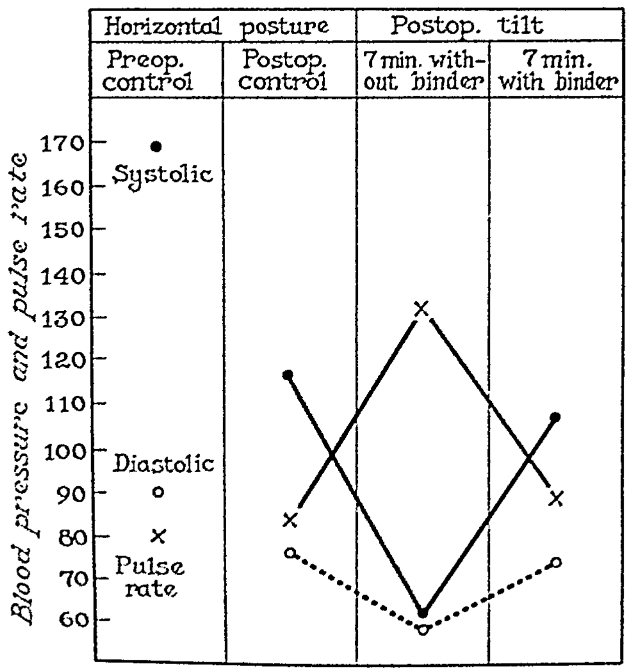

Fig. 1.—Effect of tight abdominal binder on orthostatic hypotension and tachycardia after sympathectomy in Case 1. Patient was tilted on table to 40-degree head-up posture.

In all cases after operation, release of the binder while the patient was in the head-up posture resulted in a decrease in blood pressure and increase of pulse rate, often sufficient to produce mild syncope. How much of this effect was due to reactive hyperemia and how much to other factors, such as the sudden release of mechanical support to the hypotonic intra-abdominal vascular bed, is not known. Both factors were probably present. It is interesting that patients who had the greatest degrees of postoperative orthostatic hypotension derived the most benefit from the binder. Thus, the binder appears to correct a defect that is situated, at least in part, within the abdomen, and which is an etiologic factor in the orthostatic hypotension. The most reasonable assumption is that this defect is excessive pooling of blood in the dilated, hypotonic splanchnic vascular bed. The binder probably

counteracts this tendency by indirectly supporting or compressing these reservoirs. The net effect is the establishment of a larger gradient of venous pressure between the abdomen and thorax, which results in better cardiac filling and a more favorable ratio of circulating blood volume to vascular capacity.

In Case 7 the effect of alternate tightening and release of the binder was observed while the patient was standing erect, and the results were compared with control values. As in all cases which were studied, a tightening of the binder resulted in a net increase in blood pressure, a decrease in pulse rate, and an increase in pulse pressure. Release of the binder resulted in opposite effects.

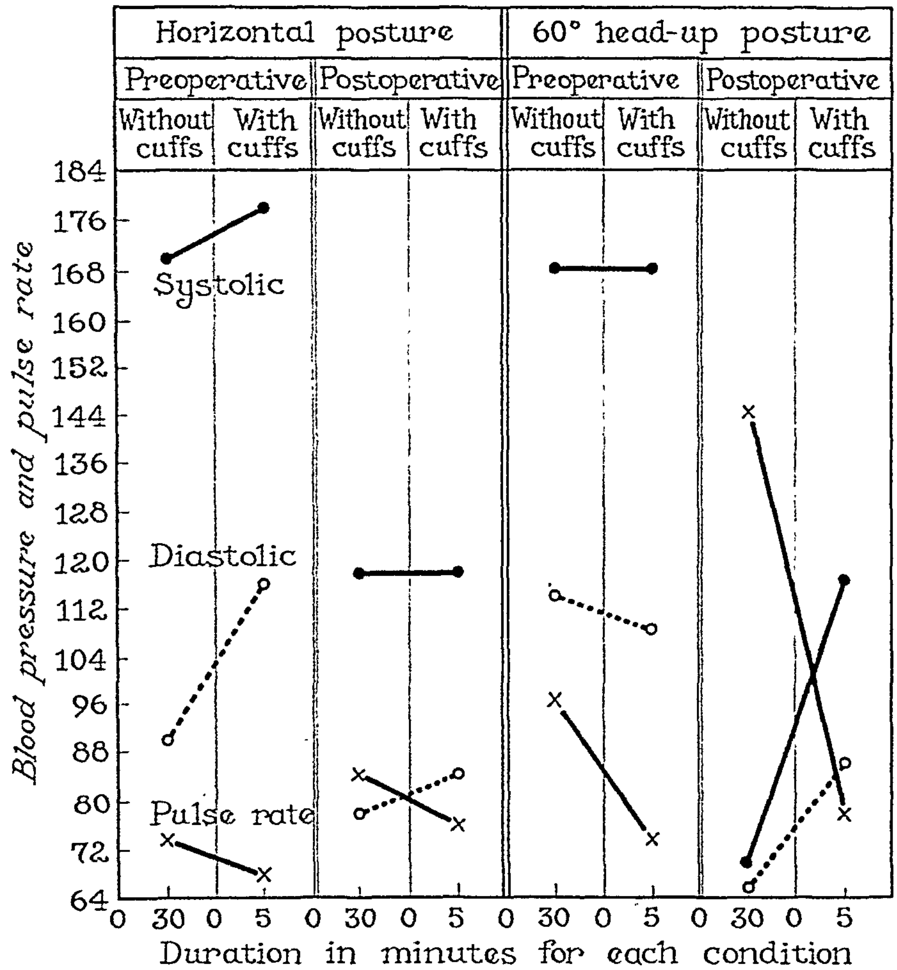

Fig. 2.—Effect on orthostatic blood pressure and pulse rate of bilateral thigh cuffs in Case 1. Patient was tilted to 40-degree head-up posture.

BILATERALLY INFLATED THIGH CUFFS

In order to study further the location of the defect responsible for orthostatic hypotension, we desired to see whether this condition could be lessened or corrected by the use of tight cuffs around the thighs, which would cut off momentarily the circulation in the legs. Stead and Ebert[10] felt that, in cases of spontaneous orthostatic hypotension, the vasoconstrictor response to a normal amount of pooling is abnormal. Other investigators have stated that perhaps there is an abnormal amount of

TABLE II

EFFECT ON ORTHOSTATIC BLOOD PRESSURE (MM. HG) AND PULSE RATE OF BILATERAL THIGH CUFFS INFLATED ABOVE SYSTOLIC PRESSURE IN THE THIGH

CASE	PREOPERATIVE								POSTOPERATIVE							
	HORIZONTAL POSTURE				60-DEGREE HEAD-UP POSTURE				HORIZONTAL POSTURE				60-DEGREE HEAD-UP POSTURE			
	WITHOUT CUFFS		WITH CUFFS		WITHOUT CUFFS		WITH CUFFS		WITHOUT CUFFS		WITH CUFFS		WITHOUT CUFFS		WITH CUFFS	
	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE
1*	170/ 90	74	178/116	68	168/114	96	168/108	74	118/ 78	84	118/ 84	76	70/ 66	144	116/ 86	78
2	200/134	84	206/150	88	190/132	96	206/130	96	164/ 88	80	160/ 84	76	140/ 76	106	146/ 82	84
3	226/140	94	218/140	96	206/136	92	218/132	100	190/134	88	204/130	86	168/110	100	206/130	94
4	166/120	80	174/136	84	156/118	92	166/134	100	150/114	84	170/130	96	136/116	128	130†/ 114†	128†
5	156/ 98	68	176/110	84	158/112	92	174/114	90	180/112	96	190/122	88	160/118	118	198/134	116
6	194/124	84	214/134	80	198/136	92	220/142	88								
7													96/ 86	140	136/122	124
8	160/108	76	190/120	76	170/112	84	176/122	84					66/ 60	112	88/ 80	84
9					138/104	80	158/110	88	190/130	100	196/126	120	166/128	108	174/140	116
Mean	182/116	80	194/129	82	173/120	90	186/124	90	165/109	89	173/113	90	125/ 95	119	149/111	103

*10-degree head-up posture was used in this case.

†Cuffs in this case were not inflated above the systolic pressure in the thigh, so that these figures in the head-up posture are not included in the final averages.

pooling of blood when such patients are placed in the head-up posture. It may be that this type of hypotension is not comparable to that which occurs after sympathectomy, for in the former the pulse usually does not accelerate to any significant degree.

Cuffs for taking blood pressure in the thighs were placed about both thighs just above the knees and inflated, while the patient was in the horizontal posture, to a point well above systolic pressure in the thigh. The patient was then moved on the tilt table to the 60-degree head-up posture, and, at the end of one minute and three minutes, the blood pressure in the arm and pulse rate were determined. One thigh cuff was then deflated, after which blood pressure and pulse rate were again determined. Then the second cuff was deflated and similar determinations were made; the patient then was returned to the horizontal posture.

Results.—Comparison with control values after sympathectomy indicates that using the cuffs resulted in an average increase in orthostatic systolic blood pressure of 24 mm., and, in the diastolic pressure, of 16 mm., with a decrease of 16 beats per minute in the pulse rate (Table II). It would appear that, in cases in which the greatest degrees of orthostatic hypotension and tachycardia occurred after operation, the blood pressure increased the most when the cuffs were employed. Thus, in Case 1 (Fig. 2), the cuffs, when the patient was in the 60-degree head-up posture, produced an increase of 46 mm. Hg in the systolic, and an increase of 20 mm. in the diastolic, pressure over the control value. The pulse rate was decreased a total of 66 beats by using the cuff. In contrast, in this case, the cuffs, when used before operation, did not produce an increase in the orthostatic systolic pressure, produced an actual decrease in the orthostatic diastolic pressure, and decreased the orthostatic pulse rate only a third as much as after operation. In all cases, release of one cuff, followed by release of the second cuff, resulted in successive decreases in blood pressure; the decline was greater after release of both cuffs than it was after release of either cuff. Obviously, effects produced by cuffs are only of academic interest, for it is not practical to use them therapeutically.

ABDOMINAL BINDER, PLUS THIGH CUFFS

Since both the abdominal binder and thigh cuffs increased blood pressure and decreased pulse rate, it seemed desirable to ascertain what effect a combination of these agents would have on blood pressure and pulse rate. They were accordingly applied and used, as previously described, on six of the ten patients, while they were in the horizontal and in the 60-degree head-up postures, before and after extensive sympathectomy.

Results.—As indicated in Table III, the combined use of these procedures on patients in the head-up posture after operation produced an average rise in systolic pressure which was twice as great as before

TABLE III

EFFECT ON ORTHOSTATIC BLOOD PRESSURE (MM. HG) AND PULSE RATE OF BILATERALLY INFLATED THIGH CUFFS PLUS ABDOMINAL BINDER

CASE	PREOPERATIVE								POSTOPERATIVE							
	HORIZONTAL POSTURE				60-DEGREE HEAD-UP POSTURE				HORIZONTAL POSTURE				60-DEGREE HEAD-UP POSTURE			
	WITHOUT CUFFS OR BINDER		WITH CUFFS AND BINDER		WITHOUT CUFFS OR BINDER		WITH CUFFS AND BINDER		WITHOUT CUFFS OR BINDER		WITH CUFFS AND BINDER		WITHOUT CUFFS OR BINDER		WITH CUFFS AND BINDER	
	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE
1*	170/ 90	74	180/126	76	168/114	96	178/120	80	118/ 80	80	126/ 80	52	70/ 66	144	130/ 92	72
2									164/ 86	80	180/ 96	80	128/ 76	100	160/ 68	88
3					200/138	88	220/134	92	190/134	88	190/128	90	166/110	100	200/130	92
4	166/120	82	194/146	100	146/120	96	180/138	98	150/114	84	166/128	84	138/116	128	144/118	104
6	194/124	84	210/130	72	198/136	92	216/142	84	Unable to do; left thigh too sore and painful							
7									172/130	112	194/132	96	96†/ 86	164	158/134	136
8									120/ 90	70	150/100	76	54/ 50	132	120/ 94	98
Mean	177/111	80	195/134	83	178/127	93	198/133	88	152/106	86	168/111	80	109/ 84	128	152/106	98

*40-degree head-up posture used.
†Tones faint, grade 3+.

operation. The average increase in the diastolic pressure was more than three and a half times as great, and the average decrease in pulse rate was six times as much after operation as before operation. Specifically, the cuffs and binder produced an average increase of 20 mm. in the systolic blood pressure before operation and 43 mm. after operation, an increase of 7 mm. in the diastolic pressure before, and of 25 mm. Hg after, operation, and a decrease in the pulse rate of 5 beats before, and 30 beats per minute after, sympathectomy. In general, the greatest increase in blood pressure and slowing of the pulse rate after operation occurred in cases of the most severe orthostatic hypotension and orthostatic tachycardia.

COMPARISON OF EFFECTS ON ORTHOSTATIC BLOOD PRESSURE AND ORTHOSTATIC PULSE RATE OF (1) ABDOMINAL BINDER, (2) BILATERAL THIGH CUFFS, (3) ABDOMINAL BINDER PLUS THIGH CUFFS, AND (4) COLD-PRESSOR TEST

The technique for the first three procedures has already been described. The cold-pressor test was done according to the technique of one of us (Hines[11]), as outlined in a previous report. As indicated in Fig. 3, when the patients were in the head-up posture before operation, the binder, thigh cuffs, binder plus thigh cuffs, and cold-pressor test produced respective average increases in systolic pressure of 7, 13, 20, and 23 mm. Hg. After operation, the blood-pressure-elevating effects of the first three agents were about twice as great, whereas the response to the cold-pressor test was unchanged, or, in cases of postoperative orthostatic hypotension and tachycardia, was even decreased. All agents except the cold water caused a postoperative rise in diastolic pressure which was two to three times greater than the effect produced preoperatively. After operation, in the head-up posture, the binder did not affect the pulse rate, whereas the cuffs decreased it an average of sixteen beats per minute, and the binder plus cuffs decreased it thirty beats per minute. The pulse rate was not counted during the cold-pressor test in any case. Patients who had the greatest orthostatic hypotension after sympathectomy derived the greatest benefit from the use of these agents. Thus, in Case 1, binder and cuffs caused a rise in systolic pressure of 10 mm. before operation and 60 mm. Hg afterward, a rise in diastolic pressure of 6 mm. before, and 26 mm. after, operation, and a decrease in pulse rate of 16 beats per minute before operation and 72 beats afterward. The cold water caused a rise of 12 mm. in systolic pressure before operation and only 8 mm. after operation.

Comment.—If discomfort were important as a cause of the elevation in blood pressure after the use of the agents named, the cold water should elevate the blood pressure, for its pressor effect is presumed to be the result of the discomfort which it induces. If discomfort were an important factor in the effects of these agents on pulse rate and

blood pressure, such marked differences would not be expected between patients who had severe orthostatic hypotension and those who did not have this phenomenon after sympathectomy.

We might suggest as a possible explanation for the good effects of the binder and cuffs on orthostatic hypotension and orthostatic tachycardia that sympathectomy apparently decreases vasomotor tonus in a large portion of the vascular bed below the level of the diaphragm.

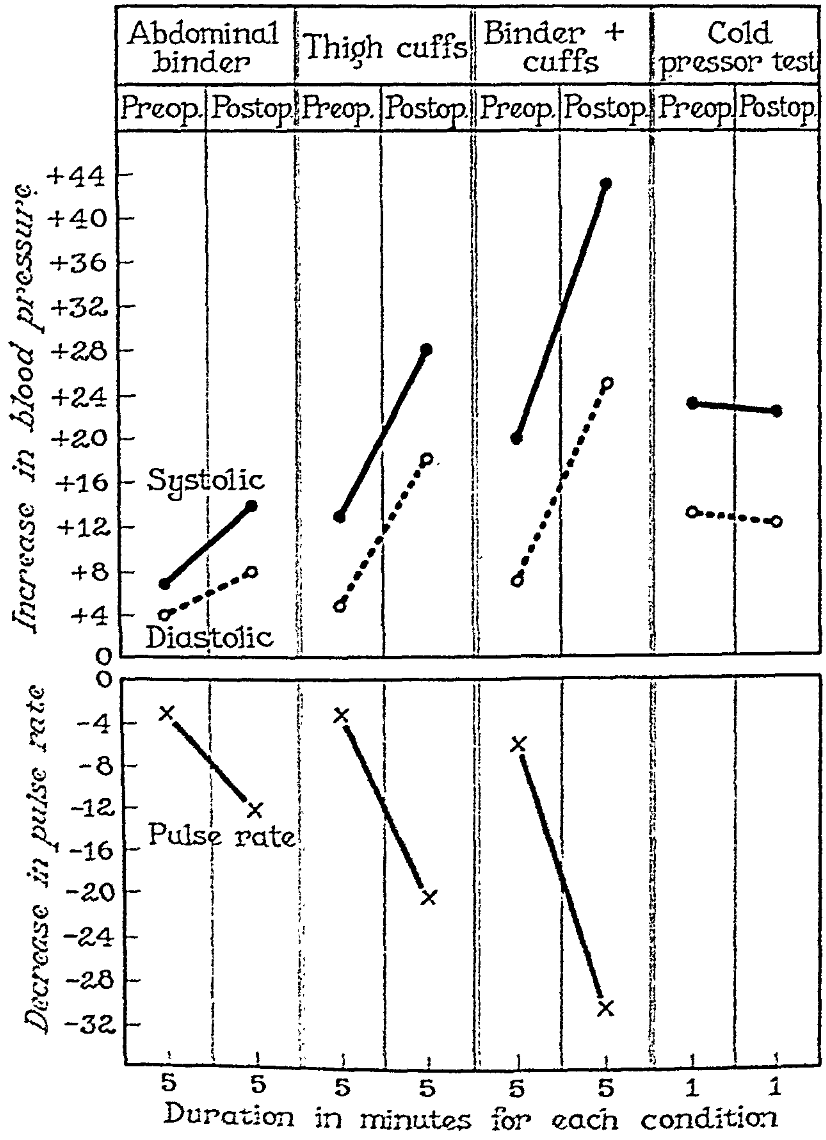

Fig. 3.—Comparative blood-pressure-raising and pulse-slowing effect of abdominal binder, bilateral thigh cuffs, abdominal binder plus thigh cuffs, and cold-pressor test before and after extensive sympathectomy. Average for all patients in 60-degree head-up posture. Values given denote deviations from control values represented by zero lines.

The vessels, as a result, become more readily distensible under the influence of the hydrostatic pressure which is brought into play by the head-up posture. The tonus which is inherent in the wall of the vessels cannot fully compensate for this force, so that, as a result,

the vessels in the regions affected by sympathectomy become more capacious, creating thereby an unfavorable disproportion between vascular capacity and circulating blood volume. The result of this would probably be an impairment in venous return and in cardiac filling, and a decrease in blood pressure and an increase in pulse rate when the patient is in the head-up posture. The increased pulse rate may be related to the decrease in blood pressure, resulting in inhibition of pressoreceptive stimuli which originate in the thoracic aorta and carotid sinuses. The marked hypotension and evidence of defective venous return to the heart seem to exclude the Bainbridge reflex as a mediator of the rapid pulse which occurs in cases of postoperative orthostatic hypotension and orthostatic tachycardia.[1] The slowing of the pulse rate, along with an increase in blood pressure when venous return is presumably improved by the use of a tight abdominal binder, supports this view. The abdominal binder probably tends partially to correct the defect responsible for orthostatic hypotension and orthostatic tachycardia by reducing the size of the splanchnic vascular resevoirs through external support to the hypotonic vessels. By this means and by the increased intra-abdominal pressure which the binder produces, the venous pressure gradient between the abdomen and thorax is presumably increased.

The cuffs, by eliminating the vascular segment below the knee, decrease the size of the vascular reservoirs and reduce the hydrostatic column against which the circulation must work while the patient is in the head-up posture. The sum total of these effects seems to be the establishment of a more favorable balance between vascular capacity and circulating blood volume, with resultant improvement in cardiac filling, cardiac output, and blood pressure. Some support for this hypothesis is afforded by the studies of Bjure and Laurell,[12] who found that, when patients with marked orthostatic tachycardia stood in water up to the level of the heart, the pulse rate did not increase. Stead and Ebert[10] made similar studies, and found that the blood pressure of patients who had orthostatic hypotension and orthostatic tachycardia was the same when they stood in water at axillary level as it was when they were in the horizontal posture. Standing in water at lower levels resulted in corresponding decreases in blood pressure. It is felt that the binder used in the present studies acted in a somewhat similar manner.

EXERCISE OF THE LEGS

It seems likely that decreased venous return to the heart is associated with the marked decreases in blood pressure and increases in pulse rate which occur when certain patients are in the upright posture after extensive sympathectomy. We wondered if active exercise of the legs, in cases in which possibly excessive pooling occurred, would counteract orthostatic hypotension by increasing venous return to the

heart. The importance of the venopressor mechanism in the circulation has been studied by Henderson and his associates.[13, 14] The role of muscle tonus in aiding venous return is well known. Freeman and Rosenblueth[15] and Pinkston and his co-workers,[16] however, noted a tendency to a decrease in blood pressure during muscular activity in dogs after total sympathectomy.

In the present study the patients stood still on the floor for three minutes. Control blood pressures and pulse rates were obtained after one and after three minutes in this position. They then rose up and down on the toes at a uniform rate of about thirty times a minute for two minutes. Blood pressures and pulse rates were obtained at the end of one and of two minutes of exercise. Within one and a half minutes after cessation of exercise, blood pressure and pulse rate were taken again. The results were compared to control values.

The effect of exercise was difficult to evaluate because it was not possible accurately to standardize the actual amount of work which was done. In two instances, exercise could not be done because the patients were on the verge of syncope at the end of the control period and had to sit down to avert syncope. Exercise apparently produced a greater increase in blood pressure before than after operation. The pulse rate during exercise increased 15 beats per minute before operation and 12 beats per minute after operation. This difference does not seem significant. In three of six cases studied, the blood pressure continued to decrease during exercise. Only in one case did the pulse rate decrease and the blood pressure increase during exercise after operation. In most cases, apparently, the good effects, if any, on the blood pressure of exercising the legs were not enough to oppose the hydrostatic pressure within vessels with decreased contractility resulting from sympathetic denervation.

PAREDRINOL SULFATE

Stead and Kunkel[17] showed that *α*-N-dimethyl-*p*-hydroxyphenethylamine sulfate (paredrinol sulfate) increases venous tone and venous pressure, slows the heart rate, and produces hypertension. We desired to see whether it would be helpful in counteracting excessive orthostatic decreases in blood pressure after sympathectomy, inasmuch as Stead and Kunkel found it beneficial in certain types of circulatory collapse. Accordingly, this drug was given in doses of 10 to 20 mg. subcutaneously in Cases 7 and 8 after a series of blood pressures and pulse rates were taken while the patients were in the horizontal and then in the erect posture. The drug was given about two weeks after the second stage of sympathectomy, after the patients had been walking around in the hospital for four or five days.

In Case 7 the orthostatic blood pressure was 54 mm. higher after using the drug, and the orthostatic pulse rate was 24 beats slower than the control rate. Whereas the patient was near syncope after stand-

ing for one minute before taking the drug, she had no such difficulty after fifteen minutes of standing after receiving 10 mg. of paredrinol sulfate. There was subjective, as well as objective, benefit from the use of the drug. She did not feel faint, and was comfortable except for mild cardiac palpitation caused by the paredrinol. The results in Case 7 are shown in Fig. 4. As will be seen, a decrease occurred in orthostatic blood pressure and an increase in orthostatic pulse rate,

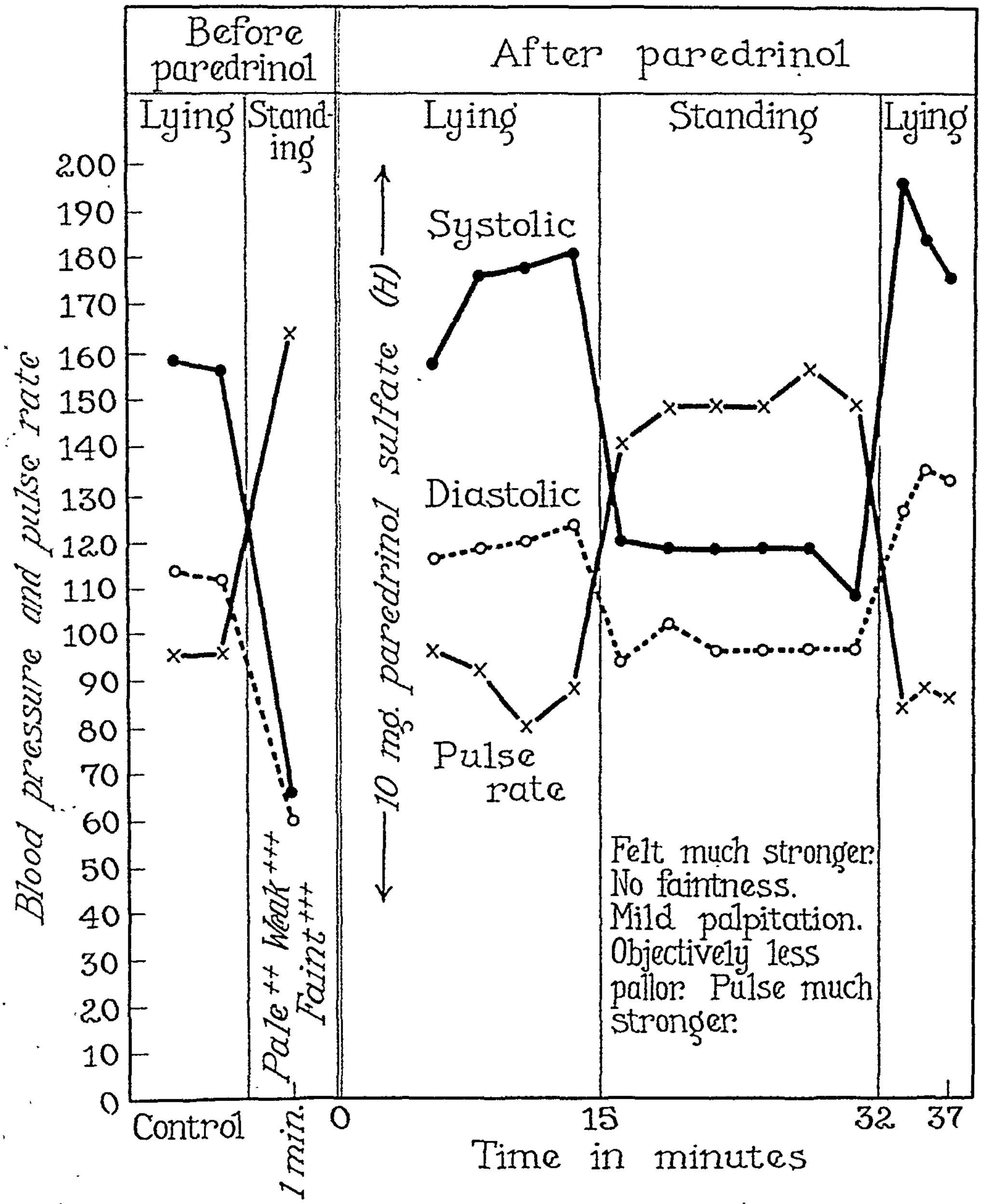

Fig. 4.—Effect of 10 mg. of paredrinol sulfate, given subcutaneously, on orthostatic blood pressure and pulse rate after sympathectomy in Case 7.

even after paredrinol had been used; the extent of these, however, was less. The level of blood pressure was raised in both postures, which seems to be the main effect of the drug. The net effect of the drug apparently was to increase the orthostatic systolic pressure 28 mm. and the diastolic pressure 20 mm., and to slow the orthostatic pulse rate 16 beats, when compared to the control values. In Case 8, the

injection of 20 mg. of paredrinol sulfate rendered the orthostatic systolic pressure 30 mm. higher and the orthostatic pulse rate 14 beats slower than the control values. It seems that paredrinol might be beneficial in counteracting excessive decreases in blood pressure when certain patients stand soon after sympathectomy, at a time when vascular adjustments are still imperfect. Stead and Kunkel found, however, that this drug tends to become less effective with repeated use.

SUMMARY AND CONCLUSIONS

Ten cases of essential hypertension were studied before and after extensive splanchnic sympathectomy. The following observations were made:

The use of a tight abdominal binder was of considerable benefit in counteracting excessive degrees of postoperative orthostatic hypotension and tachycardia. To be effective, the binder must be properly applied. The fact that the binder had little effect preoperatively or postoperatively in those cases in which orthostatic hypotension and orthostatic tachycardia were not great, but did increase the blood pressure and slow the pulse rate after operation in cases in which these phenomena occurred, suggests that the defect responsible for this condition lies, at least in part, within the abdomen.

Cuffs tightly applied above both knees in order to cut off the circulation to the legs tended to elevate the blood pressure and slow the pulse rate. This effect was greater after, than before, sympathectomy, and was greatest after operation among patients who had the greatest degrees of orthostatic hypotension and tachycardia.

The combined use of an abdominal binder and thigh cuffs had a greater blood-pressure-raising and pulse-slowing effect than either procedure alone. The effect of the tight abdominal binder, thigh cuffs, or both, in counteracting orthostatic hypotension and tachycardia was due chiefly to factors other than the discomfort which was induced by these agents.

Exercise of the legs did not produce a conclusive effect on orthostatic blood pressure and orthostatic pulse rate.

Paredrinol sulfate definitely raised the level of the postoperative blood pressure in the horizontal and erect postures, and alleviated most of the symptoms which otherwise resulted when patients were in the erect posture. It reduced somewhat the amount of orthostatic decrease in blood pressure. It may be helpful, therefore, in counteracting excessive degrees of orthostatic hypotension when patients begin to walk soon after sympathectomy.

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COMPARISON OF TOTAL VIBRATIONS OBTAINED FROM A NORMAL, RAPIDLY DYING, HUMAN HEART WITH THOSE OBTAINED IN CHRONIC MYOCARDIAL DISEASE

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WITH THE TECHNICAL ASSISTANCE OF R. E. STURM

CLINICIANS have long recognized that heart sounds may vary in quality.[1, 2] These alterations have often been defined as sounds of poor, fair, or good quality. The significance of the changes has never been well understood.

It was noted, when we were studying revived human hearts several years ago, that the heart sounds varied when the bell of a stethoscope was directly on the heart.[3] In the early period of revival the sounds were relatively long and low in pitch, and, as the ability of the heart to contract improved, they became short and higher in pitch. These observations that the sounds varied as the function of the heart improved led us to consider the advisability of recording them as a clinical method of estimating cardiac function. After study of the literature[4-6] and direct stethoscopic observations, a correlation of cardiac sounds and function seemed justifiable.

Many attempts had been made to correlate heart function with heart sounds,[7, 8] and different results were noted in the literature.[9, 10] The logical reason for such a disordered state of thought seemed to be that too much attention had been paid to the auscultatory group of vibrations and not enough to the total group. It therefore seemed advisable to record all the vibrations produced by the heart, whether audible or inaudible, rather than focus our attention on the audible group alone. It was felt that finer changes in the fundamental heart tones might be detected in such detailed study. Therefore, in order to explore this possibility, an instrument (previously described[11]) was designed with a special dynamic microphone which actuates a cathode-ray tube, the movements of which are photographed on moving paper. With such an arrangement there are no lags or overshoots, and a true reproduction of all vibrations from 1 to 500 cycles per second is obtained.

In addition to the total cardiac vibrations, the instrument records the onset of ventricular systole. Lead wires attached to the arms or arm and leg of the subject actuate the cathode-ray tube by the electrocardiographic R-wave voltage. This produces a straight vertical line in

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Presented before the Eighteenth Scientific Session of the American Heart Association, Atlantic City, June 5, 1942.
Received for publication April 26, 1943.

the vibrocardiogram at the onset of ventricular systole. The R-wave marker makes it easy to identify the cycle of the heartbeat by keeping the systolic phase oriented.[12]

A number of observations have been made with the instrument. Those by Smith, Kountz, and Edwards[13, 14] have shown that variations in vibration complexes do occur when the microphone is in direct contact with the dog's heart and the physical state of the latter is modified. The results of such controlled studies cannot be applied clinically for the reason that the chest cavity must modify the vibrations to some extent. It is necessary to establish uniformity of technique when the human heart is studied in the chest.

METHOD OF STUDY

The technique for taking records consisted of placing the subject on his back with the chest exposed, and the microphone on the thorax at any desired point. Arbitrarily we chose for this study patients whose chests were considered to be normal in contour. We used the four usual auscultation areas for obtaining total cardiac vibration curves.

In comparing the tracings of total cardiac vibrations from a large number of normal subjects and patients with outspoken or questionable heart disease, it was found that definite changes in the curves occurred when the myocardium was weakened or dilated. Briefly, these changes were characterized by a prolongation of the first vibration complex which occurred at the onset of systole and embodied the first heart sound and the appearance of large, slow, inaudible waves throughout the tracings. A preliminary study of these tracings has already been presented.[12]

In order to study these phenomena in greater detail, it was decided to approach the problem from a more basic angle. Since the heart, whether normal or diseased, attempts to adjust its output to any change in circulatory demand, a change in the force of the apex beat may often be appreciated. Tracings of total cardiac vibrations may likewise be considerably altered after activity or rest. These considerations emphasized the need of establishing a base line from which all records might be compared by first obtaining vibrocardiograms with the patient under basal conditions. The following procedure was then adopted:

A group of normal persons (100) and another group of patients with definite myocardial disease, hypertensive and coronary disease (35) were selected. A third group of 30 patients who were suspected of having early myocardial disease, or who had debilitating disease which might affect the myocardium, was also chosen. Each patient was asked to appear at the laboratory before breakfast and to lie down for an hour before the basal vibrocardiogram was recorded. After the record was obtained, the subject was given moderate exercises, and another record was taken. In all cases the tracings were obtained from the aortic, tricuspid, mitral, and pulmonic areas, and are shown in that order in the curves. The position of the pickup unit of the vibrocardiograph was

carefully marked on the patient's chest when the basal curves were obtained; the unit was placed at exactly that point when the record was made after exercise.

THE DYING HEART

In a further analysis of the influence on the curves of the physical and functional state of the heart, it seemed to us important to follow a normal human organ through its agonal period. We were able to make such an observation on a convict who died in the lethal gas chamber at the Missouri State Penitentiary. In this instance the subject was sitting when the control and agonal records were taken. Because of the straps which held the patient in the chair, the pickup was placed over the mitral area only. In addition to the vibrocardiogram, the second lead of the electrocardiogram was taken. In the observation on the convict's heart we could trace the development of myocardial weakness under conditions of anoxemia.

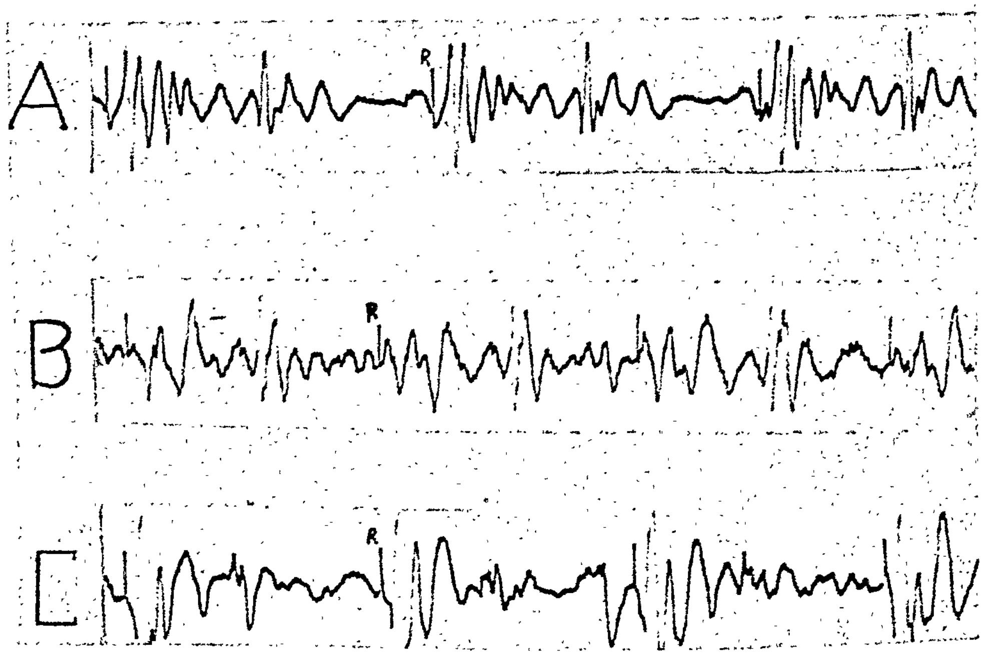

Fig. 1.—Curve *A* shows a controlled vibrocardiogram of the convict. The R-wave markers are indicated. Marked sinus arrythmia was present. The heart rate was about 95 beats per minute.

Curve *B* was taken 20 seconds after exposure to cyanide. There was an increase in heart rate to about 110 beats per minute, and slight spreading of the second component of the first vibration complex occurred.

Curve *C*, taken 30 seconds after exposure to cyanide, shows slight slowing of the heart (rate, 87). There is definite spreading of both the first and second complexes, with the loss of some of the finer vibration waves. There is, in addition, a quickening of the heart beat, and the second sound approaches closer to the first. Low frequency vibration waves are noted.

RESULTS

Fig. 1, Curve *A*, shows the control record which was taken over the mitral area on a person who was dying under conditions of anoxemia. The first sound, as in all normal records, may be divided into two

phases. The first consists of the two major vibration waves which immediately follow the electrocardiographic R wave and fall in the early part of the first sound. They are relatively high and steep, and represent the first audible portion of this heart sound. The second phase consists of waves of less frequency and amplitude. A steplike decline is thus fairly characteristic of the first sound over the mitral area.

Curve *B*, obtained 15 seconds after exposure of the convict to cyanide, shows a widening of the first phase of the first vibration complex. A slight change in the position of the man's head occurred at this point. The body position was not changed. Additional waves developed in midsystole, and some increase in heart rate occurred.

Curve *C*, taken 45 seconds after exposure to hydrocyanide acid gas, shows a further increase in the height of the first vibration component of the first complex, and a relative decrease in the second sound. There is some increase in auricular vibrations.

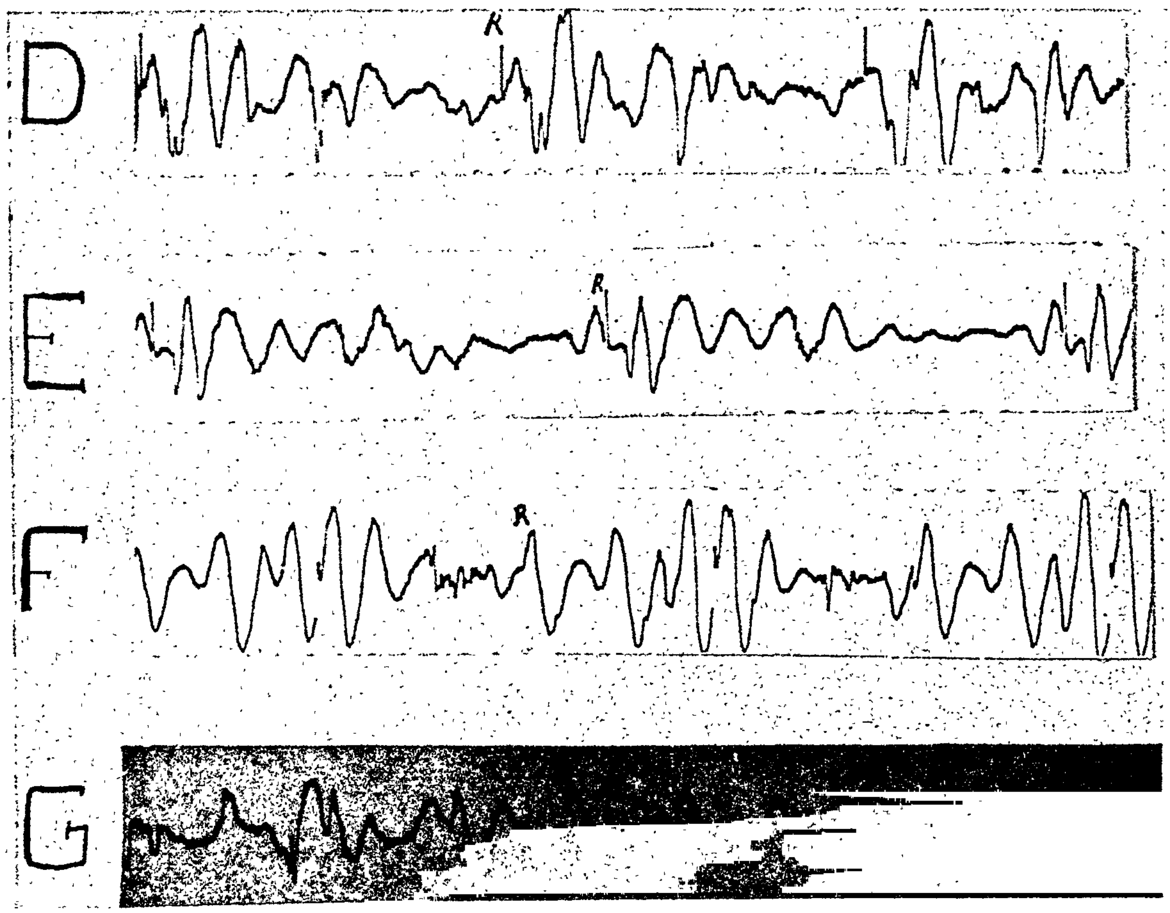

Fig. 2.—Curve *D*, taken one minute after exposure to cyanide, shows a definite spreading of all the first vibration complexes, with a negative movement of the cathode-ray as it approaches the second sound.

Curve *E*, taken 1½ minutes after exposure to cyanide, shows the development of low-frequency waves with each heart beat. The R waves may be seen preceding systole.

Curve *F*, taken 2 minutes after exposure to cyanide, is difficult to analyze, but, compared to the synchronized electrocardiogram, the R wave falls at the point labelled *R*. Throughout the contraction phase of the heart, low-frequency waves are seen. The second heart sound is masked by a gross slow movement of the cardiac vibrations. The finer vibrations are considered to be respiratory in origin.

Curve *G*, taken 2½ minutes after exposure to cyanide, shows the terminal gross movements of the heart. Relatively few vibrations are present. The fogging of the curve is due to the ammonia gas which was introduced into the chamber to neutralize the hydrocyanic acid gas.

Fig. 2, Curve *D*, shows a definite spreading of the first and second components of the first sound complex. The second sound has increased in intensity and its components have widened. This feature, however, was not consistent, and, since some respiratory spasm was present, may have been due, in part, to the changes in the air content of the chest.

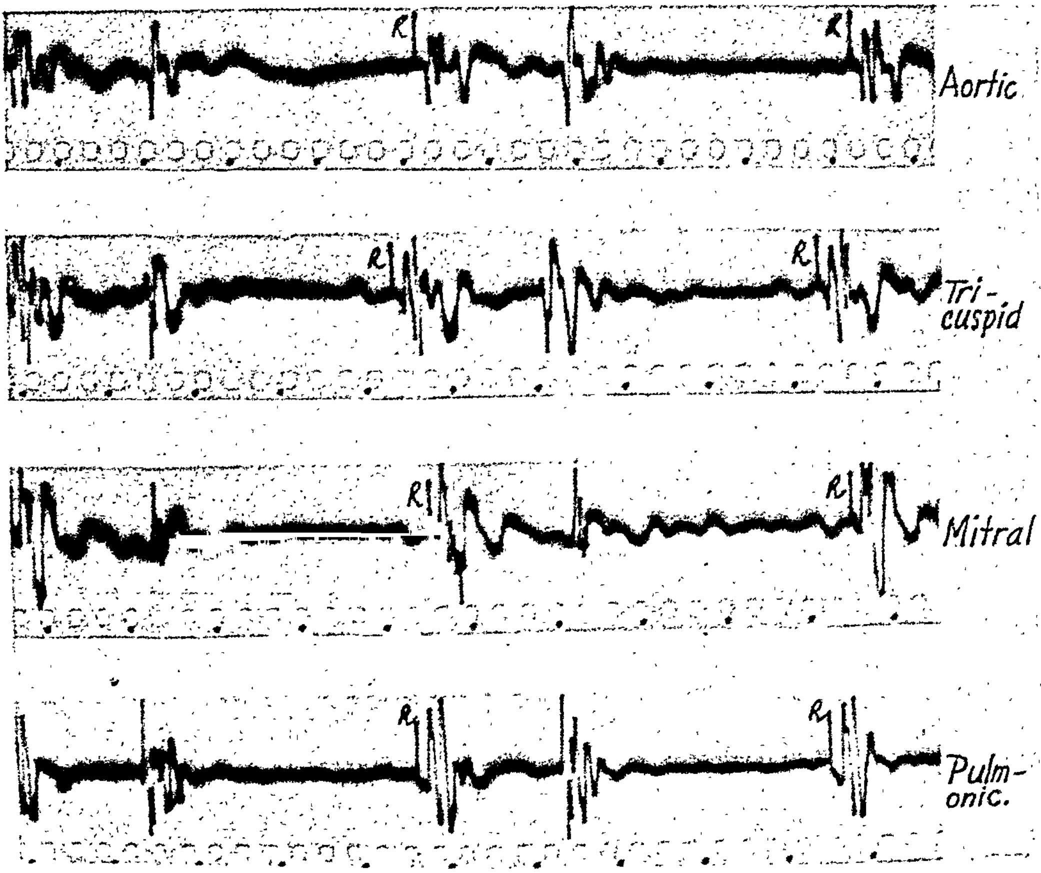

Fig. 3*A*.

Figs. 3*A* and 3*B*.—Vibrocardiograms of a normal subject under basal conditions and after activity. The auscultation areas from which the record was obtained are indicated. The R-wave markers are indicated on each curve.

Curve *E*, taken 2½ minutes after exposure, shows definite slowing of the heart. In the first complex there are loss of the first vibration components and an apparent widening by fusion of the first and third ones. Low frequency waves may be seen coming in at this point. The first change noted in the electrocardiogram occurred at this time, and appeared rather suddenly as a lowering and flattening of the T wave.

Curve *F*, taken 3½ minutes after exposure to cyanide and 30 seconds after the final respiratory effort, shows low frequency systolic and diastolic waves. These waves are not unlike those found in experimental animals and in patients with acute coronary artery occlusion.

Fig. 3 shows the vibrocardiogram of a normal subject under basal conditions and after activity. Definite changes of two types may be seen in the curve. First, the initial vibration complex, beginning with ven-

tricular systole, is more sharply defined after activity, and, compared with the normal curve, the vibration group as a whole tends to be of slightly lesser duration. These particular changes almost invariably occur in tracings from normal subjects. Occasionally one sees low-frequency waves in systole and diastole, often most prominent at the aortic or tricuspid areas. In the present series, this occurred in five cases.

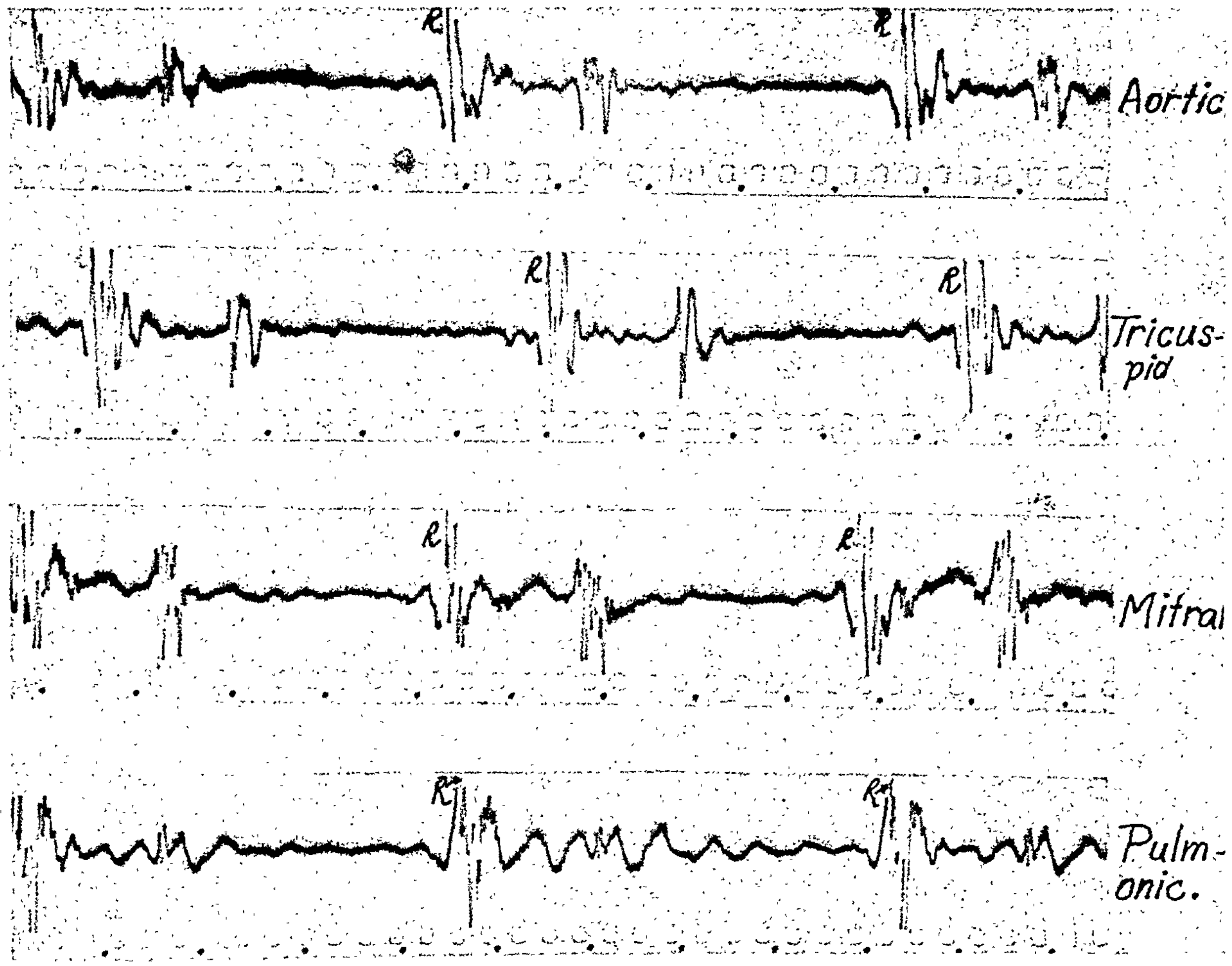

Fig. 3B.

However, when there are low frequency waves in the basal curves, they tend to diminish or disappear entirely in the tracings after activity. From an examination of the curves, one finds that, in persons who appear to be normal, activity results in an intensification of the first vibration complex, which becomes sharper and more steep, and is broken by quick movements of the beam. The second heart sound vibrations likewise become sharper by virtue of an increase in blood pressure.

Vibrocardiographic curves from patients with myocardial disease (hypertrophy and dilatation) showed constant modifications.

A typical curve from this group of patients is shown in Fig. 4. The curve was obtained from a 66-year-old woman who had been treated for gall bladder disease, but had suddenly suffered extreme precordial pain, a gradual fall of blood pressure, and fever. Electrocardiographic studies, made at that time, showed definite evidence of myocardial in-

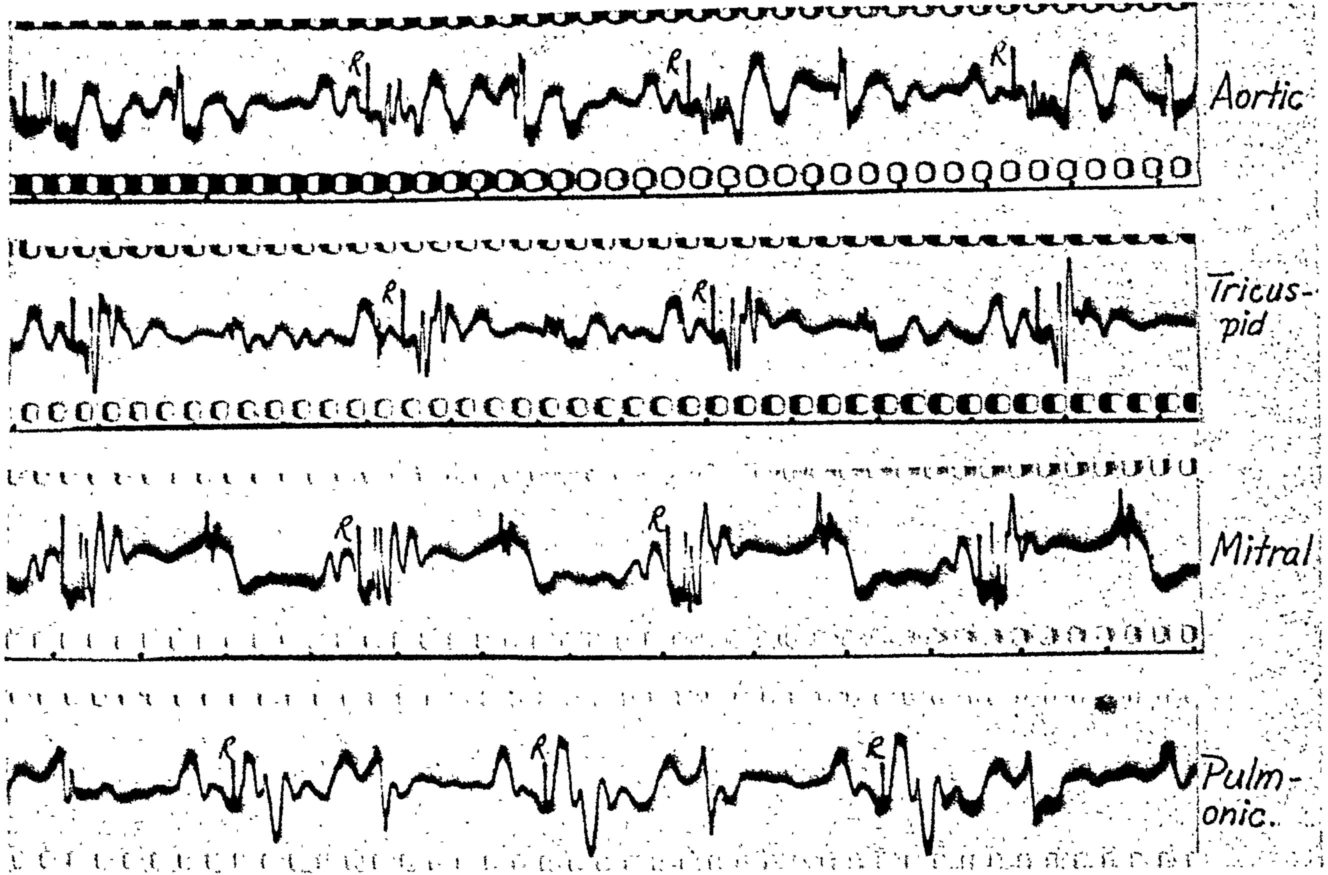

Fig. 4A.

Figs. 4A and 4B.—Fig. 4A shows the vibrocardiogram of a patient who had had myocardial infarction (taken under basal conditions). Fig. 4B is the record taken after activity. The R-wave marker and auscultation areas from which the tracings were obtained are indicated. Note the low-frequency elements in the basal curve and their accentuation after activity in all the tracings.

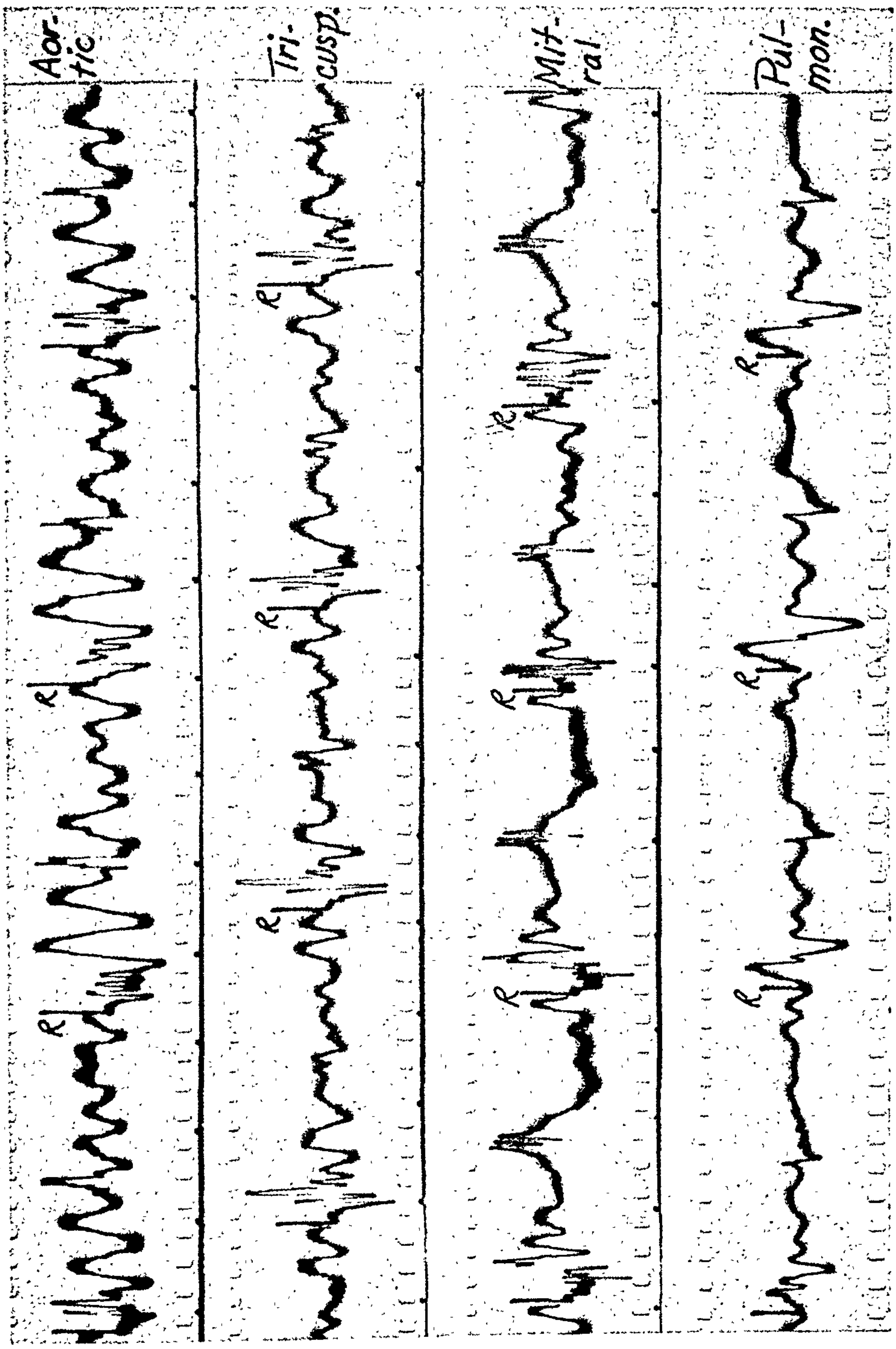

Fig. 4B.

farction. A kymogram six weeks later revealed no general cardiac enlargement, but showed reduced excursions of the heart and aneurysmal dilatation of the left ventricular wall. The vibrocardiogram which was taken under basal conditions was in marked contrast to a normal curve (Fig. 3). The most interesting feature of the tracing is the prominence of large, low-frequency waves which dominate the first and second vibration complex. As clearly shown in the illustration, the complexes appear spread, with rounded peaks. Indeed, when one listens to such a heart the first sound often seems muffled and distant and of "poor quality." When the patient had been "active" throughout the morning, the changes in the curves were usually even more accentuated. The low-frequency, inaudible waves became more prominent, and the first vibration complexes were more blunt and spread. The entire tracing appeared to consist largely of rounded waves and low amplitude ripples of various frequencies. These changes in the conformity of the curve persisted even though the pulse rate was at nearly the same level as when the patient was under basal conditions.

Patients who showed changes in the vibrocardiograms alone make up our third group. This group, consisting of 30 patients, presented symptoms which pointed to some myocardial impairment, but were not severe. Ten of the patients suffered from a mild form of angina pectoris. The others had rheumatic or syphilitic heart disease or showed evidence of early cardiac weakness associated with hypertension. Some had severe anemia or infection, without definite clinical evidence of cardiac disease. Vibrocardiographic records were obtained on all of these patients before, or immediately after, treatment had been instituted.

In some of these patients, "abnormal" changes were evident in the curves taken under basal conditions, but, in others, alterations in the curves were brought out only after the patients had been active.

Fig. 5 shows a typical instance of these changes in the vibrocardiographic curves from a subject with no clinical evidence of heart disease. This patient, a 28-year-old white woman, was under treatment for primary anemia, syphilis, and general undernutrition. At the time the record was made the erythrocyte count was 3,000,000, and the hemoglobin was 63 per cent. The kymogram showed that the heart was of normal size, with excursions of essentially normal scope. The electrocardiogram was considered indeterminate. The curve of total cardiac vibrations which was taken under basal conditions showed somewhat abnormal contour of the deflections; the first vibration complexes were tall and somewhat spread. After activity, the curves recorded from the same locations on the chest wall were definitely altered. The first vibration complexes were marked by slopes of lesser steepness, and large, inaudible waves occurred in systole and diastole. The latter simulated the changes seen in advanced myocardial disease, and were not unlike some of the waves recorded from the dying human heart. Since it is

Fig. 5*A*.

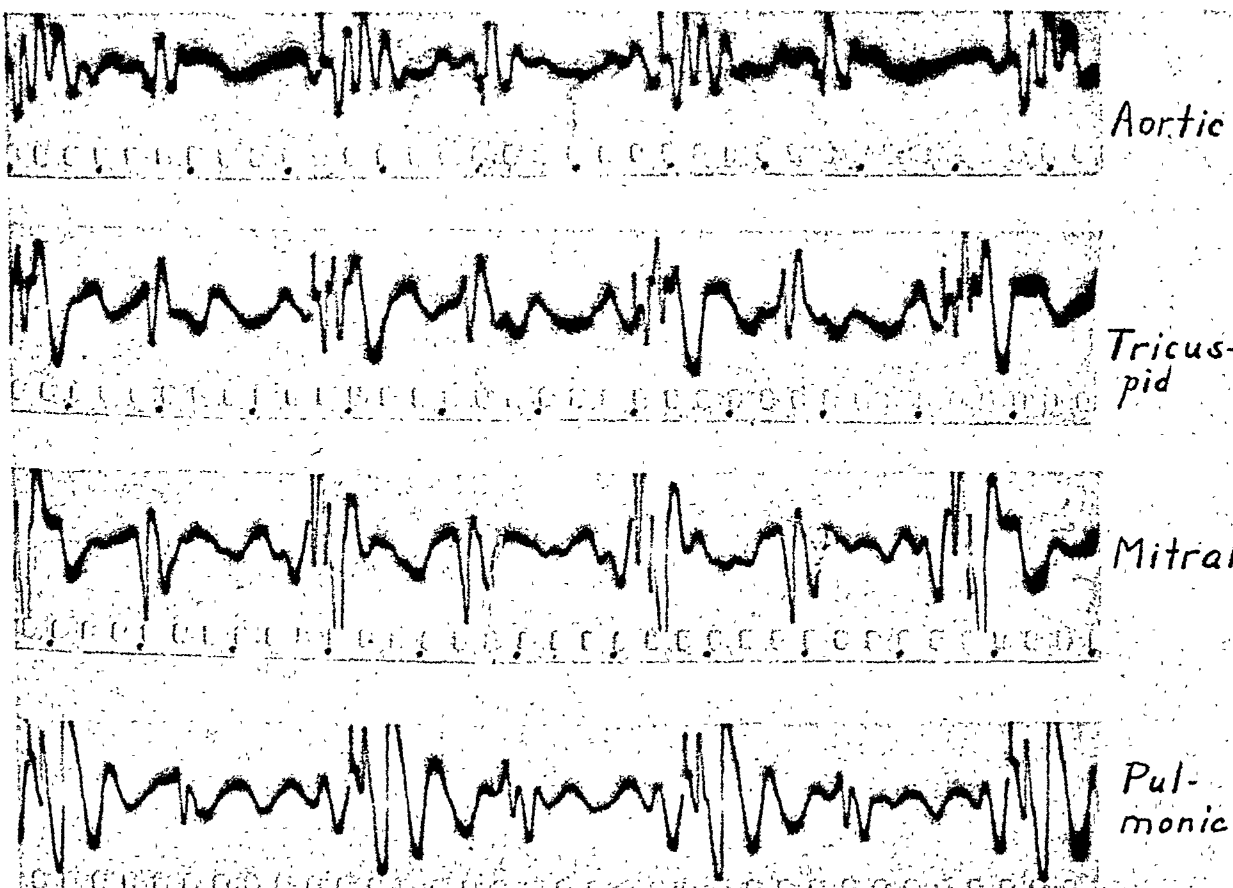

Fig. 5*B*.

Figs. 5*A* and 5*B*.—Fig. 5*A* is a vibrocardiogram of a patient who had only slight clinical evidence of heart disease. The corresponding auscultation areas and R-wave markers are indicated. After activity (Fig. 5*B*), the low-frequency waves became more prominent, and there was some spreading of the first vibration complex in the aortic and tricuspid areas.

known that the heart may suffer from one or all three of the debilitating conditions which this patient presented, it was considered probable that these alterations were due to secondary changes in the heart muscle.

DISCUSSION

One should not forget that total cardiac vibrations may be expected to differ from heart sound vibrations alone. The type of curve and the component parts are entirely different. The inherent difference between total cardiac vibration records and audible records should be borne in mind when one attempts to analyze the curves.[15]

The normal vibrocardiogram, from any auscultation area, consists of vibration components which may be roughly divided into two dominant vibration groups.

The first group of deflections immediately follows the R-wave marker, and begins with the onset of ventricular contraction. The vibrations are tall and peaked, with steep slopes which represent the audible element of the first heart sound. The second heart sound, which is caused by closure of the semilunar valves, is recorded as a group of sharply pointed deflections, sharper in profile and of somewhat lesser duration than the first vibration group. A number of small "preliminary waves" frequently occur in advance of the first vibration (just preceding the R-wave marker), and are thought to be due to auricular contraction; the preliminary waves are usually best seen in tracings from the tricuspid area. In about 5 per cent of normal tracings, very low frequency ripples, below auditory level, occur. In most curves, these low, smooth undulations seem to be in phase with each other and with the onset of systole. The phenomenon is usually more prominent in persons who are debilitated. It is in the character of these low-frequency, inaudible waves that the most striking changes occur in myocardial disease.

It is to be emphasized that, in our cases, the changes in vibration complexes and the appearance of large, slow waves in patients who were known to have myocardial disease were frequent before the institution of therapy. As our vibrocardiographic studies progressed, it became evident that patients who had suggestive or outspoken signs of myocardial disease, but showed no other laboratory abnormalities indicating cardiac abnormality, often exhibited changes in the total vibration curves. The changes went so far as to be comparable to those from patients with definite heart disease. Some patients who had no signs of heart disease, but were suffering from severe anemia or infections which affect the heart muscle, frequently showed vibrocardiographic changes.

The variation of total vibrations of the heart when the physical and functional state declines is established. The dying human heart under conditions of anoxemia produces a continuous change in the pattern of total cardiac vibration curves. These vibration complex curves have a general resemblance to those obtained from the precordial area of patients with heart disease.

The chest does modify the experimental and clinical cardiac vibration curves. The chest factor is, however, fairly constant, and, provided the shape of the chest is normal, and respiration is quiet, only minor variations are attributable to respiratory factors. An extreme variation in the relationship of the heart to the chest wall does modify cardiac vibrations, and precaution should be taken to eliminate this influence. The curve of the total cardiac vibrations from a normal chest without respiratory effort has been sufficiently constant to be considered standard, and thereby to establish a general pattern, as has been previously reported.

The fact that the cardiac vibrations are extremely sensitive to variations in the physical and functional state of the heart suggests the possibility of their use in the early recognition of heart disease. Our observations indicate that changes in vibrations occur early in heart disease, and suggest that further study and clinical correlation should be directed to establishing their value in early heart disease. Attempts must be made to bring the degree of cardiac and chest activity to a minimum. Hence the basal state is important. Changes in the curves produced by graded, increased activity of the subject throws light on a heart's ability to respond to an increased load. Such changes in the total cardiac vibration curves as spreading of the first complex, decrease in the amplitude of the first complex, and development or increase of low frequency waves during systole or diastole occur when the work of the heart is increased.

SUMMARY

The curves of total cardiac vibrations, recorded by means of a cathode-ray tube, were obtained from a dying convict's heart, from persons who were known to be normal, from patients with heart disease, and from persons who were suspected of having heart disease. The changes in the total cardiac vibrations from the dying human heart and from patients with heart disease have similar features. Spreading, especially of the first and second components of the first complex, was noted. Low-frequency systolic and diastolic waves developed under both clinical and experimental conditions, and suggested, as had been previously suspected, disordered cardiac function.

The authors wish to express their appreciation to Paul E. Kaiser, Warden of the Missouri State Penitentiary, and to the many officials who made possible part of this study.

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THE DELAYED DIASTOLIC MURMUR ASSOCIATED WITH VENTRICULAR ECTOPIC BEATS. PHONOCARDIOGRAPHIC STUDIES

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PROVIDENCE, R. I.

IT IS well known that when ventricular ectopic beats occur early in diastole, the diastolic phase of the normal beat is replaced by the ectopic beat. However, under these same conditions in mitral stenosis and aortic insufficiency, in which there is a diastolic murmur, there is a delay in the appearance of the murmur. The diastolic murmur is now found during the diastolic phase of the ventricular ectopic beat. This same delay will probably be found in diastolic murmurs associated with corresponding lesions of the tricuspid and pulmonary valves. If one is not acquainted with this delay in the appearance of the murmur after the normal beat, one may think that all the sounds heard during ventricular extrasystoles are part of the ectopic beat.

Phonocardiograms were taken to illustrate the delayed murmurs. The first illustration was taken with the electrocardiogram as a reference tracing (Fig. 1). Sound tracings were taken at the apex to show the delayed diastolic murmur in mitral stenosis. The second set of records was made at the same area, with the apex cardiogram as a reference tracing (Fig. 2). The third set was taken at the second right intercostal space to show the delayed diastolic murmur in aortic regurgitation (Fig. 3). In this set the jugular tracings were used for reference.

The upper phonocardiograms in each set were made by the stethoscopic method, and the lower by the logarithmic method described by Rappaport and Sprague.[1] The numbers *1* and *2* indicate the first and second heart sounds, and *s.m.* and *d.m.* indicate the type of murmur.

All of the records were made on the same patient. He was a 27-year-old white man who had mitral stenosis and insufficiency as well as aortic stenosis and insufficiency. The electrocardiograms showed auricular fibrillation, ventricular ectopic beats from multiple foci, coupling, and right axis deviation. He had had too much digitalis. After the digitalis was stopped, the etcopic beats disappeared. At this time he had the usual murmurs in their regular places.

It is to be noted that there was an accentuation of the mitral diastolic murmur during the rapid inflow of blood into the left ventricle in the diastolic phase of the ectopic beat.

From the Rhode Island Hospital and Providence Lying-In Hospital.
Received for publication April 23, 1943.

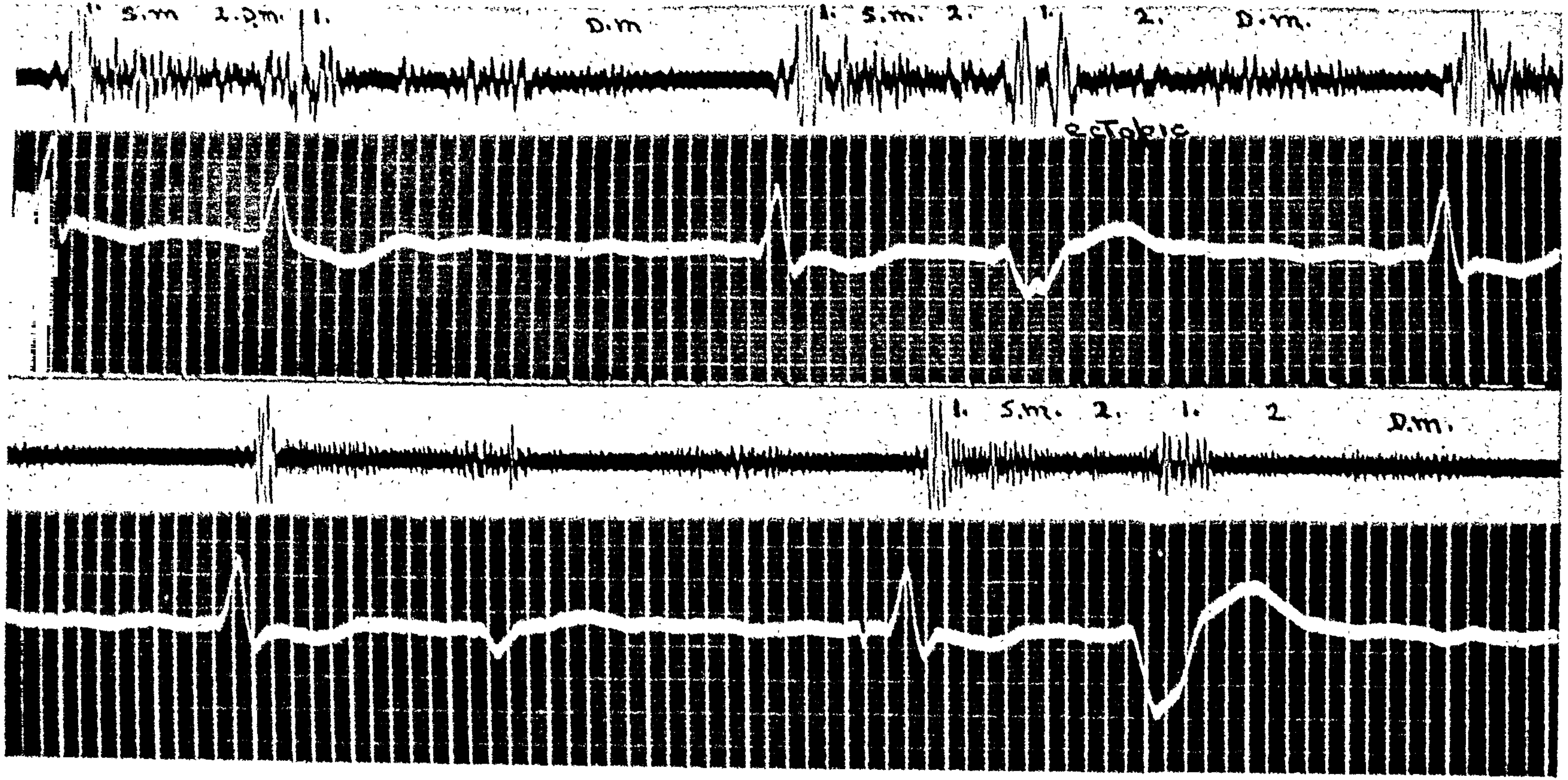

Fig. 1.—Phonocardiograms with the electrocardiogram as reference tracing. The upper record was made by the stethoscopic method and shows the low frequency sounds best. The lower record was made by the logarithmic method. The sounds recorded by this method are within human audibility and are similar to those heard when using an acoustic stethoscope. Note the diastolic murmur during diastole of the ectopic beat.

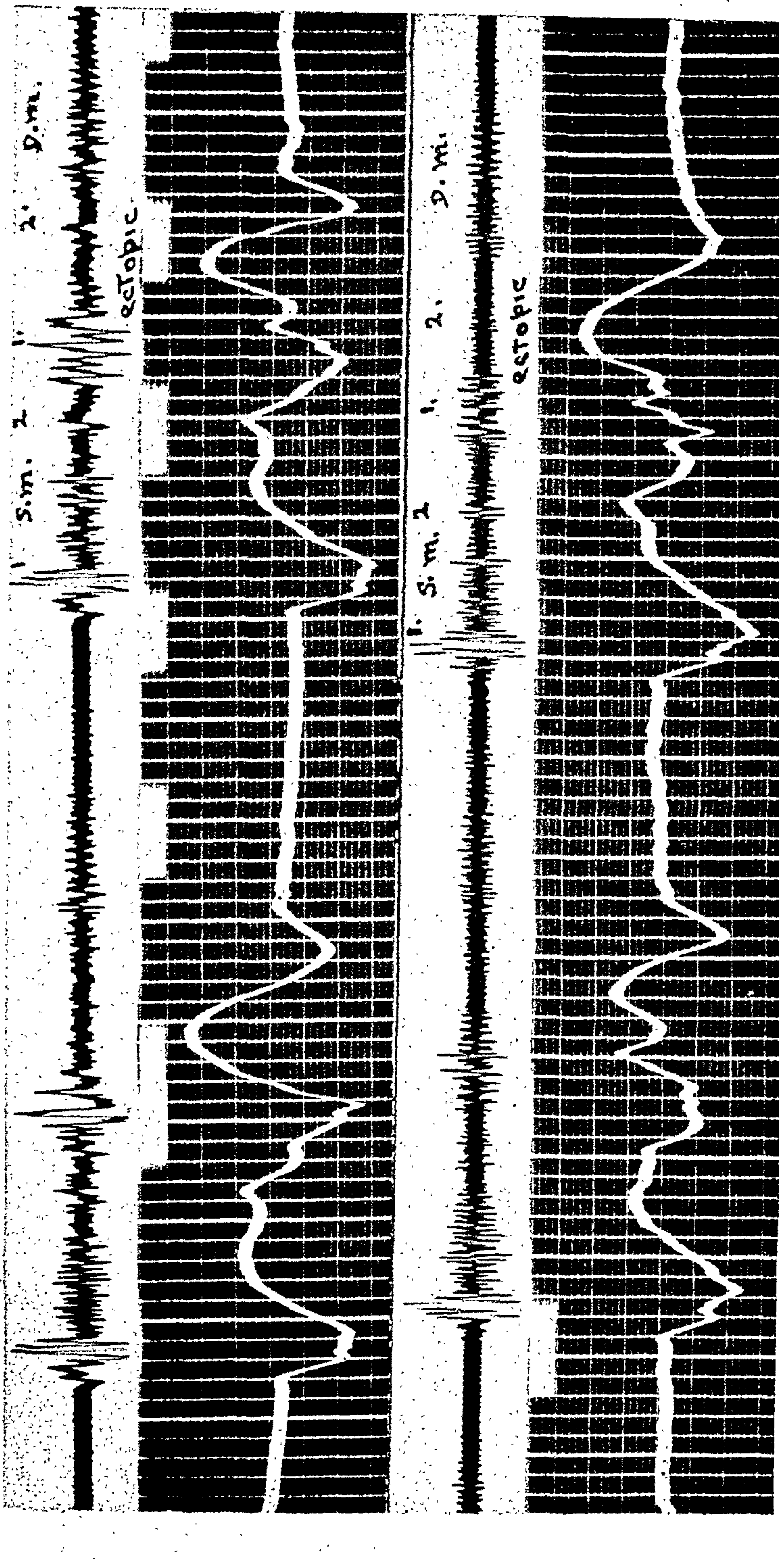

Fig. 2.—Phonocardiograms and apex cardiograms (linear tracings). The upper record was made by the stethoscopic method and the lower by the logarithmic method. The delayed mitral diastolic murmur is shown during the diastolic phase of the ectopic beat. The murmur begins at a definite interval after the second sound. It is loudest during the time of rapid inflow.

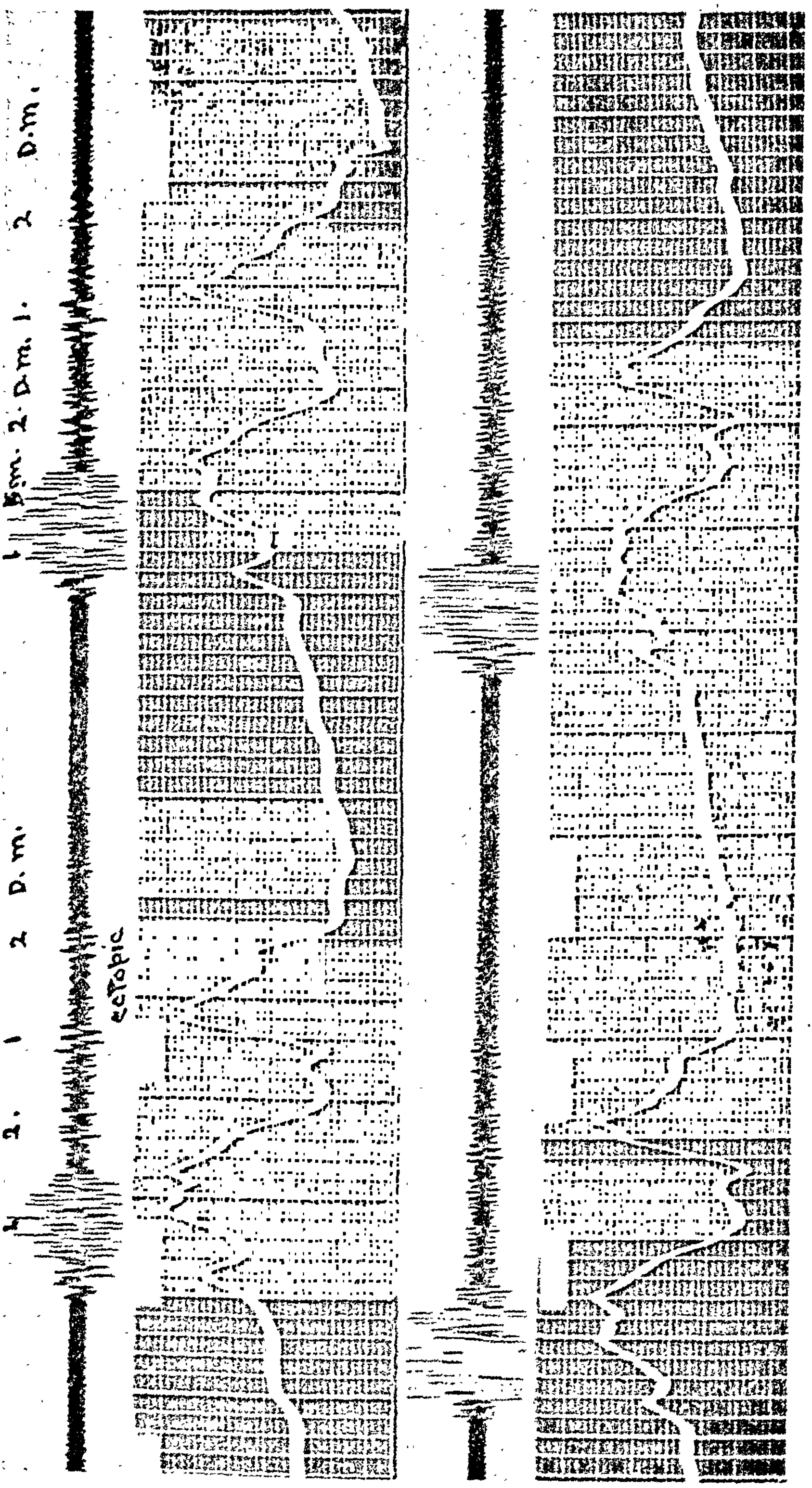

Fig. 3.—Phonocardiograms and Jugular tracings. The upper record was made by the stethoscopic method. The lower record was made by the logarithmic method. The phonocardiograms are from the second right intercostal space. Note the aortic diastolic murmur in the diastolic phase of the ectopic beat. It is continuous with the second sound.

This same accentuation has been noted during the time of rapid inflow in mitral stenosis without ectopic beats. There is also an increase of loudness at the time of the auricular beats. Pericardial friction rubs show the same characteristics. Therefore, in interpreting phonocardiograms, as well as electrocardiograms, one should know the clinical findings.

Although there was aortic regurgitation in this case, the predominant murmur at the apex was that of mitral stenosis. The murmur began a short interval after the second sound, and occurred for the most part in the diastoles of the ectopic beats because of the coupling in this case. The aortic diastolic murmur was of higher frequency, and followed directly after the second sound in the ectopic beats, just as it does with normal sinus rhythm.

The low frequency murmur was best illustrated in the tracings made by the stethoscopic method. Since the aortic diastolic murmur was of higher frequency, it was best seen in the tracings taken by the logarithmic method.

SUMMARY

By a delayed diastolic murmur is meant a murmur that cannot come at its usual time in diastole because of the occurrence of ventricular ectopic beats. Therefore, the murmur is delayed until the diastolic phase of the extrasystole.

This delayed murmur is usually not recognized because it comes so long after the normal beat, and the sounds are associated with the ectopic beat itself.

Phonocardiograms were made to illustrate this point in both mitral stenosis and aortic regurgitation.

The possibility that such delayed diastolic murmurs may also be associated with lesions of the right side of the heart is suggested.

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Clinical Report

MYOCARDITIS CAUSED BY EPIDEMIC PAROTITIS

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MAJOR JOHN NOLL, JR., MEDICAL CORPS
ARMY OF THE UNITED STATES

INTRODUCTION

EPIDEMIC parotitis has been recognized as a clinical entity since antiquity, and such complications as orchitis, meningoencephalitis, and pancreatitis have been reported by many medical observers since that time. However, it was not until 1918 that attention was first called to the possibility that myocarditis might result therefrom. In that year, Pujol,[1] a French military surgeon, described three cases in soldiers, in which, because the patients developed dyspnea or substernal pain after recovery from mumps, he suspected that the myocardium had been affected by that disease. Unfortunately, no electrocardiographic studies or other corroborative data were available at that time. In 1932, the examination of post-mortem material prompted Manca[2] to state "the mumps virus can attack the heart, and the lesion consists of an acute interstitial myocarditis, especially characterized by a fibrinous exudate which differentiates it from other forms of myocarditis, and may be considered as a peculiarity of this infection"; this definitely established the possibility of cardiac complications in mumps. Nevertheless, the electrocardiographic demonstration of such a complication during the convalescent period of mumps has, until now, been lacking. For this reason a cardiac survey of fifteen soldiers who were recovering from this illness was undertaken by the authors. In this group, one instance of acute myocarditis was discovered. This is described in detail because its importance is obvious, not only to civilian practitioners, but also to military surgeons who encounter mumps in the epidemic proportions which it frequently assumes in time of war.

CASE REPORT

A 19-year-old soldier was admitted to the Station Hospital, AAFTTC Chicago, March 23, 1943, because of a swelling under the left side of the jaw and in front of the right ear. This swelling had first been noted by the patient the day before. He had otherwise been well. His past medical history was essentially unimportant, and he never suffered from joint pains, chorea, or heart disease. Physical examination at the time

From the cardiac section of the medical service, Station Hospital, AAFTTC, Chicago, Ill.

Received for publication July 5, 1943.

TABLE I

DATE	SIGNIFICANT ELECTROCARDIOGRAPHIC DATA	REMARKS	DAY OF DISEASE
3/30/43	Heart rate, 48; flattening of T_2; inverted T_3; P-R, 0.16 sec.	Temperature normal; clinical examination of heart negative; parotid swelling almost entirely absent: no arthritic manifestations	8th
4/ 4/43	Heart rate, 68; T_2 upright; T_3 diphasic; P-R, 0.16 sec.	Temperature normal; all parotid swelling has disappeared; clinical examination of heart negative; no arthritic manifestations	13th
4/ 8/43	Heart rate, 63; T_2 upright; T_3 diphasic; P-R, 0.16 sec.	Temperature normal; teleoroentgenogram reveals normal heart; clinical examination of heart negative; no arthritic manifestations	
4/13/43	Heart rate, 68; T_2 upright; T_3 diphasic; P-R, 0.28 sec.	Temperature 100° F. all day; clinical examination of heart negative; sedimentation rate, 42 mm. in one hour; no arthritic manifestations	
4/14/43	Heart rate, 83; T_2 upright; T_3 diphasic; P-R, 0.28 sec.	Temperature normal; sedimentation rate, 34 mm. in one hour; no arthritic manifestations; clinical examination of heart negative	
4/17/43	Heart rate, 68; T_2 upright; T_3 upright; P-R, 0.32 sec.	Temperature normal; sedimentation rate, 25 mm. in one hour; clinical examination of heart negative; no arthritic manifestations	
4/23/43	Heart rate, 80; T_2 upright; T_3 upright; P-R, 0.20 sec.	Temperature normal; sedimentation rate, 20 mm. in one hour; no arthritic manifestations, clinical examination of heart negative	
5/ 4/43	Heart rate, 68; T_2 upright; T_3 diphasic; P-R, 0.16 sec.	Temperature normal; sedimentation rate, 12 mm. in one hour; no arthritic manifestations; clinical examination of heart negative	
5/18/43	Heart rate, 70; T_2 upright; T_3 diphasic; P-R, 0.18 sec.	Temperature normal; sedimentation rate, 10 mm. in one hour; no arthritic manifestations; clinical examination of heart negative	

TABLE II

EFFECT OF ATROPINE SULFATE (GR. 1/25) ADMINISTERED INTRAMUSCULARLY

INTERVAL AFTER EXHIBITION OF ATROPINE SULFATE	ELECTROCARDIOGRAPHIC DATA
Control (before injection of drug)	Normal sinus mechanism; P-R, 0.30 sec.; heart rate, 83
10 minutes after	Auriculoventricular dissociation; auricular rate, 79; ventricular rate, 88
20 minutes after	Normal sinus mechanism; P-R, 0.24 sec.; heart rate, 107
30 minutes after	Normal sinus mechanism; P-R, 0.28 sec.; heart rate, 125
40 minutes after	Normal sinus mechanism; P-R, 0.36 sec.; heart rate, 142

of his admission was essentially negative except for a slight, spongy swelling over the right parotid region and under the left side of the jaw. There were no significant abnormalities of the heart. The diagnosis of mumps was confirmed by the medical officer in charge of the

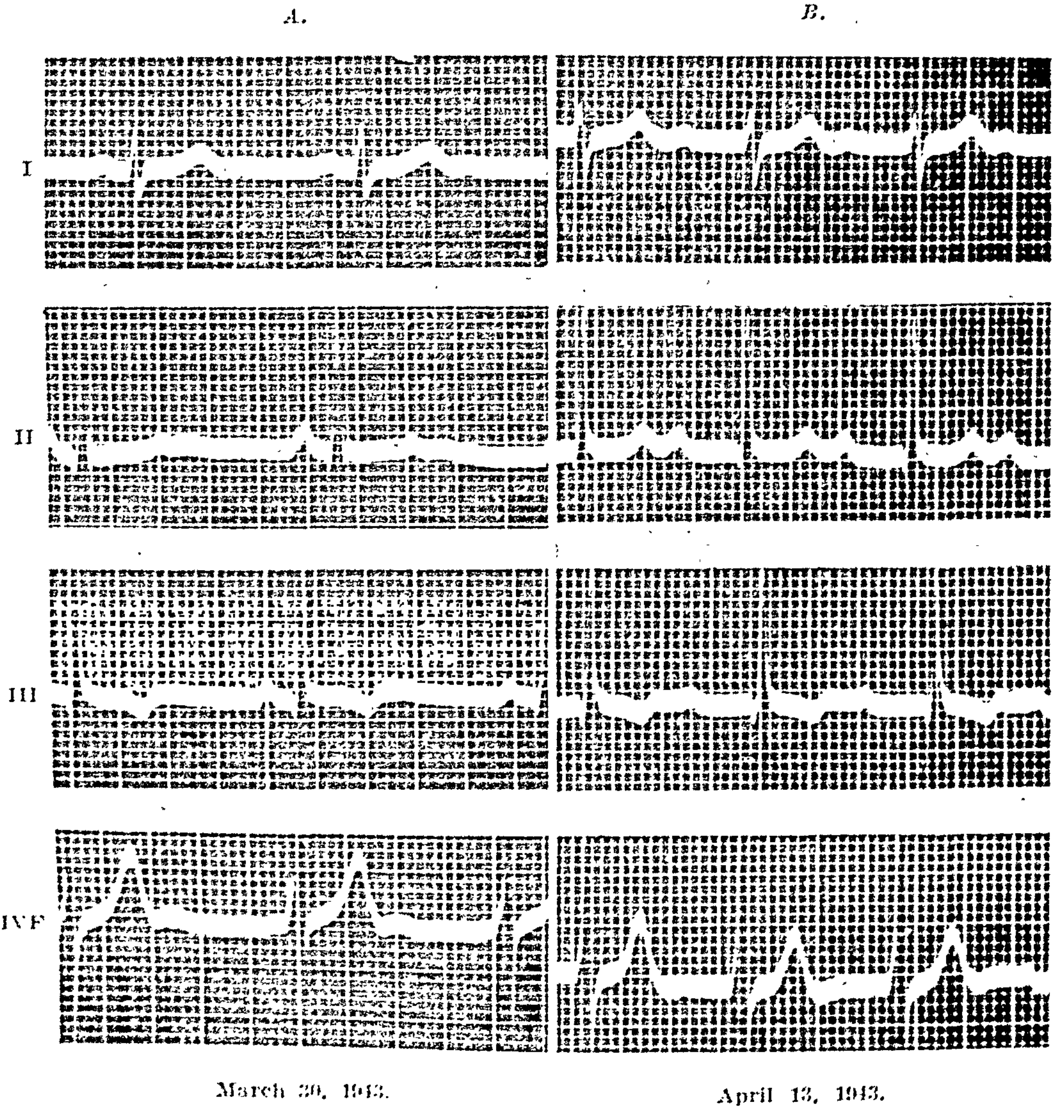

Fig. 1.

contagion ward. The patient's progress in the hospital was uneventful, as attested by the following notes:

March 24, 1943.—Swelling in the original area has increased a little. No new involvement. No complications.

March 27, 1943.—Swelling is subsiding. No new involvement. No complications.

March 29, 1943.—Swelling continues to subside. No complications.

April 2, 1943. All swelling has disappeared. No complications.

April 4, 1943.—Uneventful convalescence

On March 30, 1943, a routine electrocardiogram was obtained (Fig. 1, *A*). It will be noted that the only abnormalities consist of flattening of the T wave in Lead II and sinus bradycardia. In a subsequent electrocardiogram, five days later, the abnormal T pattern and bradycardia had disappeared. On April 13, 1943, the electrocardiogram showed first degree A-V heart block, with a P-R interval of 0.34 second (Fig. 1, *B*). Other records were obtained at frequent intervals, and the data from these tracings are summarized in Table I. The effect of atropine sulfate on the delayed A-V conduction was observed April 15, 1943, and the results of this experiment are recorded in Table II. The last electrocardiogram, which was obtained May 18, 1943, was entirely normal, and the patient was returned to duty May 22, 1943.

During the entire period of his hospitalization the patient never presented any symptoms suggestive of cardiac disease. No other complications of mumps occurred. He never complained of joint pains. The temperature remained normal during most of the hospital stay; it was elevated only in the early phases of the disease. The range of the body temperature and of the erythrocyte sedimentation rate, in relation to the clinical course and the electrocardiographic manifestations of active myocarditis, is recorded in Table I. The heart shadow in two teleoroentgenograms was not abnormal. The blood pressure was never elevated.

DISCUSSION

The diagnosis of acute myocarditis as a complication of mumps can hardly be questioned in this instance, even though clinical signs and symptoms of cardiac disease were lacking. The T-wave changes and the sinus bradycardia in the original tracing might be considered of equivocal significance, but the definite, although transient, prolongation of the P-R interval surely supports such a diagnosis. In addition, the temporary shortening of the A-V conduction time produced by atropine (Table II) is a type of response similar to that which occurs in cases of first-degree heart block secondary to active rheumatic carditis.[3-5] It is, therefore, reasonable to suppose that a myocarditis of the type described by Manca[2] was probably the cause of the electrocardiographic alterations in this case. So far as we are aware, this is the first reported instance in which excessive vagal tone was shown to contribute to prolongation of the P-R interval when the latter was the result of nonrheumatic myocarditis; this emphasizes the nonspecific nature of this particular electrocardiographic abnormality.

The incidence of cardiac complications in cases of mumps may be higher than is ordinarily supposed, inasmuch as significant electrocardiographic changes were found in one of fifteen soldiers with the disease. This figure may possibly be modified in future surveys of larger numbers of subjects. It is therefore planned, if possible, to investigate this phase of the problem more intensively during the next epidemic of the disease.

It is also of interest that the myocarditis under discussion occurred without any clinical signs or symptoms, and developed independently of

any of the usual complications of mumps. This implies that perhaps many instances of this complication have been overlooked in the past. It will be noted (Table I) that it was associated with an increased erythrocyte sedimentation rate. Therefore, it is recommended that this laboratory procedure be used routinely in every case of mumps during convalescence, and, if the rate is elevated, an electrocardiogram should be obtained to establish or eliminate the possibility of a complicating myocarditis.

SUMMARY AND CONCLUSIONS

1. The first known case of myocarditis complicating mumps, in which the diagnosis was established during life, is described.
2. The importance of the routine use of the electrocardiograph in the diagnosis of this complication is emphasized.
3. The similarity of the electrocardiographic changes to those which result from acute rheumatic myocarditis is demonstrated and briefly discussed.
4. The asymptomatic nature of the myocarditis and its occurrence in the absence of the usual complications of mumps are emphasized. Attention is also called to the possibility that, for this reason, many such cases are overlooked.
5. It is suggested that, in the absence of the usual complications, a persistent increase in the erythrocyte sedimentation rate in cases of mumps, after the parotid swelling has subsided, justifies the routine use of the electrocardiograph to eliminate the possibility of a complicating myocarditis.
6. In a random selection of fifteen cases of epidemic parotitis, the incidence of complicating myocarditis was found to be 6.7 per cent.
7. Wider use of the electrocardiograph in cases of mumps in various stages of the disease is recommended in order to establish definitely the incidence of cardiac complications, and hence the optimum period for complete convalescence.
8. Our experience in this case indicates that functional recovery from myocardial involvement in mumps may be complete.

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5. Wendkos, M. H., and Noll, J.: A Survey of Rheumatic Fever in a Large Station Hospital, M. Clin. North America 28: 124, 1944.

Abstracts and Reviews

Selected Abstracts

Hueper, W. C.: Experimental Studies in Cardiovascular Pathology. IX. Reactions in the Blood and Organs of Dogs on Intravenous Injection of a Solution of Glycogen. Arch. Path. **36:** 381, 1943.

A solution of glycogen injected intravenously into dogs in single or in repeated doses elicits hematic reactions characteristic of the macromolecular hematic syndrome (primary transitory leucopenia, secondary myeloid leucocytosis, anemia, accelerated erythrocytic sedimentation, increased clotting time).

The livers of such dogs show hydropic swelling and fatty infiltration of the liver cells and a negligible amount of glycogen. The aorta and the myocardial and renal arteries exhibit intimal and medial lesions of a proliferative and degenerative nature.

Repeated intravenous introduction of glycogen is not a harmless procedure.

AUTHOR.

Dauber, D. V., and Katz, L. N.: Experimental Atherosclerosis in the Chick. Arch. Path. **36:** 473, 1943.

Forty-three 3-month-old cockerels were divided into four groups. One group received liberal amounts of an adequate diet for six months. A second group received the same diet plus cottonseed oil. The third group was placed on restricted feeding, and the fourth group received 2 per cent cholesterol in cottonseed oil, added to the basic mash. Every cholesterol-fed chick acquired atherosclerosis of the thoracic and the abdominal aorta and of the major branches. Atherosclerosis of the splenic and the coronary arteries likewise resulted. The lesions showed accumulation of lipoid-containing foam cells, fibrosis, deposition of cholesterol crystals, calcification, and cartilage formation. No foam cell atheroma or calcification developed in any chick not fed cholesterol, but the cockerels not fed cholesterol showed a high incidence of intimal fibrosis of the abdominal aorta with or without lipoid.

It is, therefore, concluded that: Atherosclerosis with intimal thickening by accumulation of foam cells, fibrosis, calcification, and deposition of cholesterol can be produced in the omnivorous chick by cholesterol feeding. Feeding of cottonseed oil alone does not produce atheroma. Simple underfeeding will not cause vascular atheroma. The earliest spontaneous vascular lesion in the white Leghorn cockerel is intimal fibrosis of the abdominal aorta with and without lipoid. Foam cells enter the intimal vasa vasorum of the thoracic aorta in cholesterol-fed chicks. The working hypothesis advanced for the genesis of these lesions is applicable also to spontaneous atherosclerosis.

AUTHORS.

Bartlett, W. M., and Carter, J. B.: Combined Electrocardiography, Stethography and Cardioscopy in the Early Diagnosis of Heart Disease. Ann. Int. Med. **19:** 271, 1943.

Combined graphic and cardioscopic diagnosis in conjunction with the routine clinical examination constitutes a practical plan for the early recognition of heart disease.

The results of combined electrocardiography, stethography, and cardioscopy in the examination of 1,108 cases of heart disease are reported and discussed.

A simplified chest lead technique is described. Chest lead abnormalities occurred in 29 per cent of the cases. These abnormalities were directly proportional to the age of the patient, being found in 20 per cent of those between 31 and 41 years of age, and in 47 per cent of those between 61 and 87 years of age.

Organic heart murmurs are usually associated with heart sound abnormalities and often with changes in the electrocardiogram. Graphic methods are of value in differentiating organic and functional murmurs.

A diastolic murmur may be confused with a systolic murmur when the first heart sound is inaudible.

A stethogram is essential for the accurate diagnosis of gallop rhythm.

A stethogram differentiates a presystolic murmur from a "roughened" first sound.

In 88 per cent of 1,108 cases, clinical findings coincided with graphic findings.

In 12 per cent of 1,108 cases, the stethogram was essential for the diagnosis of gallop rhythm, of early mitral stenosis, or of early aortic disease.

Of 102 cases of gallop rhythm, 42 per cent were misjudged clinically so far as timing the extra sound was concerned.

A double-beamed cardioscope for the instantaneous visualization of stethogram and electrocardiogram is predicted as a diagnostic adjunct in the rapid examination of recruits, applicants for flight training and for insurance, and in screening for unrecognized heart disease.

Six typical cases are reported. Results of clinical examination, correlated with graphic findings, demonstrate the value of the method for the early diagnosis of heart disease.

Serial stethograms, like serial electrocardiograms, are useful in following the course of heart disease. A comparison of records from the same patient or from other cases with the same disease is frequently of value.

Cardioscopy as well as *combined stethography and electrocardiography* aids in teaching, since visual impressions are always superior to verbal descriptions.

This method of diagnosis is young but it will grow. Stethography has already arrived at a stage comparable to electrocardiography during the third decade of its development.

AUTHORS.

Joselevich, M.: Prolonged P-R Interval and Auricular Fibrillation. Rev. argent. de cardiol. 10: 96, 1943.

Of nineteen cases of auricular fibrillation an electrocardiogram could be obtained showing sinus rhythm, the P-R interval measured more than 0.21 second in fifteen, and was normal in four.

Auricular fibrillation was persistent in eight and transient in eleven. Of the eight patients with chronic auricular fibrillation, three had mitral disease, three congestive heart failure, one had toxic goiter, and one had no demonstrable cardiac disease. Of the eleven patients with transient auricular fibrillation, one had Basedow's disease, one had syphilitic aortitis, one had pericardial effusion, one had myocardial infarction, and seven cases were of undetermined origin.

When the electrocardiogram showing normal sinus rhythm was obtained, nine patients were under digitalis treatment (eight had a prolonged P-R interval) two had recently been operated upon for a partial thyroidectomy (one had a prolonged P-R interval), and the only patient who was receiving quinidine showed also a prolonged P-R interval.

AUTHOR.

Hoff, H. E., and Nahum, L. H.: A Comparison of the Configuration in the Electrocardiogram of Endocardial and Epicardial Extrasystoles. Am. J. Physiol. 140: 148, 1943.

The configuration, in Leads I and III of the electrocardiogram, of ventricular extrasystoles elicited by stimulation of points on the endocardium and the immediately opposite epicardium, has been studied.

The direction of initial deflections of endocardial and epicardial extrasystoles was the same in both Leads I and III over most of the surface of the heart. These regions included: (1) the area over the septum, both anterior and posterior; (2) an area on the lateral margin of each ventricle, which is referred to as the center of the ventricle because it is equidistant from the septal margins; and (3) the entire surface of the right ventricle.

The direction of initial deflections in Lead I of the epicardial and endocardial extrasystoles was also found to be the same over the entire posterior portion of the right ventricle and the anterior part of the left ventricle.

The direction of initial deflections in Lead III of epicardial and endocardial extrasystoles was the same over much of the posterior portion of the right ventricle and the anterior part of the left ventricle.

Two areas were found, of the anterior left ventricle toward the left lateral border and the posterior right ventricle toward the right lateral border, where the initial deflections of endocardial extrasystoles were opposite to those of extrasystoles from immediately overlying epicardial points.

These oppositely directed initial complexes of extrasystoles elicited from such regions of the endocardium were shown to arise, as do the similar complexes from stimulation of nearby epicardial points, from excitation of the opposite ventricle.

AUTHORS.

Riseman, J. E. F., and Smith, H. W.: Some Legal Aspects of Heart Disease and the Electrocardiogram. I. Nature and Volume of American Litigation Involving the Heart. Ann. Int. Med. 19: 81, 1943.

The authors have endeavored in this paper to show what are the main sources of cardiac litigation, to point out basic legal principles important to the problem of proof, and to analyze type cases where electrocardiography might be used in court. In doing this, the authors have sought to stress important positive uses of the *electrocardiogram* while at the same time pointing out great variation in the probative value of the new species of evidence depending on the individual cardiac condition involved. They have stressed, as others have done, the interdependence of electrocardiographic interpretation on sound clinical examination and judgment. It is necessary to shatter any illusions that the electrocardiogram has universal diagnostic authority. It is only by recognizing the critical limitations of a new species of evidence that courts may protect against abuse and injustice likely to arise from extravagant claims regarding its virtue as proof.

AUTHORS.

Wilburne, M., and Langendorf, R.: The Significance of the Electrocardiogram With Prominent S Waves in Leads, I, II, and III. J. Lab. & Clin. Med. 28: 303, 1942.

Electrocardiograms exhibiting prominent S waves (final inverted phase of the QRS complex measuring 25 per cent or more of the upright phase) in Leads I, II, and III were present in 84 cases of 1,850 consecutive electrocardiograms reviewed.

In 41 of these cases definite electrocardiographic abnormalities, such as left ventricular preponderance, right ventricular preponderance, combined right and

left ventricular strain, myocardial infarction, and nonspecific abnormal patterns were found. In eight others, questionable abnormalities were present.

In 35 cases no other deviations from the normal pattern were observed, and these were regarded as the otherwise normal S type of electrocardiogram. The criteria employed in this deduction are described. In nineteen of these cases no demonstrable heart disease was present; in three the clinical findings were inconclusive; and in thirteen there was clinical evidence of heart disease.

It is concluded that electrocardiograms exhibiting prominent S waves in Leads I, II, and III are more common in patients with evidence of heart disease than in normal persons in the population of an electrocardiographic laboratory. However, in an otherwise normal electrocardiogram the S type may be a normal variant, but before this decision is made the case should be thoroughly investigated.

AUTHORS.

Glazebrook, A. J.: Eisenmenger's Complex. Brit. Heart J. 5: 147, 1943.

A case presenting the clinical and radiographic features of the Eisenmenger complex is described, and the etiology and prognosis briefly described.

AUTHOR.

Saphir, O.: Myocarditis in Bronchiectasis. Arch. Int. Med. 72: 775, 1943.

A type of myocarditis occurs in patients with bronchiectasis. It was found at autopsy eight times among 152 patients and caused unexpected death three times. Clinically, myocarditis was diagnosed in only one instance. The most significant clinical observations in these patients was a discrepancy between the relatively slight elevation of temperature and the high pulse rate. Bronchiectasis with the incumbent severe inflammatory changes constitutes a primary focus to which myocarditis can be ascribed. Also in some patients with bronchial asthma who die suddenly, myocarditis may be a contributory cause of the sudden death. From this study it is clear that in many instances a correct diagnosis as to the presence or absence of myocarditis can be made only if many sections are cut from the myocardium and most carefully examined for the specific purpose of either finding or ruling out myocarditis.

AUTHOR.

Price, R. K., and Janes, L. R.: A Case of Subendocardial Infarction. Brit. Heart J. 5: 134, 1943.

A case of coronary arterial disease is described. It was observed to progress through the stages of angina pectoris, coronary insufficiency, and cardiac infarction to a fatal termination four months after the onset of symptoms. Detailed clinical and cardiographic evidence was obtained during life, and a careful examination of the heart was made after death. A type of infarct is described that may correspond to a muscle grouping in the ventricle rather than to the distribution of a main coronary vessel.

AUTHORS.

Koletsky, S.: Acquired Bicuspid Aortic Valve With Obliteration of the Commissural Raphe. Arch. Path. 36: 602, 1943.

The acquired bicuspid aortic valve with obliterated commissural raphe probably represents a further stage of the acquired bicuspid aortic valve with retracted horizontal raphe. In the four cases described, the obliterated commissure was identified by means of the aortic media-annulus fibrosus relationship.

The lesions are usually of rheumatic origin. Conclusive stigmas of rheumatic disease were found in the heart in three cases, while in one case there were probable stigmas, limited to the aortic valve.

In three cases the aortic valve showed calcific disease with stenosis. Bacterial endocarditis was present in two cases.

AUTHOR.

Shoun, A. N.: Rheumatic Heart Disease in Arizona. Southwestern Med. 27: 140, 1943.

The author reports on rheumatic fever and rheumatic heart disease in a limited area of southern Arizona. That rheumatic fever exists in Arizona as an endemic disease is not open to question. It is found in children who have been born and reared there and continues to occur in them as well as in those who come to Arizona with or without the disease. The report is based on a study of 690 children in the school population. Of these, there were 39 who showed some abnormality of the heart. An estimation is made of the number of cases of heart disease in the state, based on these figures. The author believes that heart disease in the areas in question is the same as in other centers throughout the country.

AUTHOR.

Camp, P. D., and Galvin, L. F.: Rheumatic Fever and Rheumatic Heart Disease in Virginia. Virginia M. Monthly 70: 397, 1943.

The authors review briefly certain available statistics from different parts of the country concerning the incidence of rheumatic fever and its mortality.

A survey was made by one of the authors, in 1940, on 979 children of school age in the city of Richmond. Four hundred and sixty-six of these children were white, and 513 were Negroes. Of the white group, 2.3 per cent presented findings of organic heart disease, whereas 8.5 per cent of the Negro group presented such evidence. These figures were in no way considered scientifically accurate, but merely served to indicate a general idea of the incidence of possible heart disease in such a group.

From May 1, 1940, to July 1, 1942, 254 children were referred to the State Rheumatic Fever Program Clinic for suspected rheumatic fever and heart disease. Of this group, a definite diagnosis of rheumatic fever or rheumatic fever heart disease was made on 97 cases, or 34.2 per cent. The diagnosis of possible and potential heart disease was made in 53, or 20.8 per cent.

During the year 1940-1941, the Medical College of Virginia Hospital Division admitted on all services a total of 22,968 cases. Of this number 193 cases, or 0.84 per cent, were diagnosed as rheumatic fever or rheumatic heart disease.

Symptoms and signs of the disease and method of diagnosis are reviewed. It is the impression of the authors that the manifestations of rheumatic fever in Virginia are frequently mild and indefinite, often requiring repeated examinations before a definite diagnosis can be made. Despite these mild manifestations, many cases develop severe unequivocal rheumatic heart disease in later life. In the authors' experience, initial attacks are often ushered in by gastrointestinal upsets with abdominal pain, nausea, emesis, and sometimes diarrhea. Nosebleeds are frequent. Subcutaneous nodules and erythematous rashes are relatively uncommon. Joint symptoms in the large majority of cases are either mild or absent altogether.

Treatment of the disease is briefly discussed. It is emphasized that it is just as important to promote a return to normal activity of those children with *inactive* rheumatic fever as it is to stress rest for those children manifesting active infection.

AUTHORS.

Decherd, G. M., Jr., and Herrmann, G. R.: Rheumatic Heart Disease in Texas. Texas State J. Med. **39:** 229, 1943.

The low and further decreasing incidence of rheumatic heart disease in the South and particularly in Texas seems to be substantiated in these studies.

Further surveys from the midwestern, southwestern, western, and northwestern areas of Texas seem highly desirable for the purpose of ascertaining those factors which alter the incidence, course, and prognosis of rheumatic disease there. Certainly, further studies are needed from the Gulf Coast and from the low altitude and high altitude areas of the Southwest in an attempt to identify the factors which mollify the disease here. The slight recent increase in the number of cases of rheumatic fever and heart disease seen in the diagnostic clinic, inaugurated in 1939, is most likely the result of increased state-wide interest.

AUTHORS.

McClendon, S. J.: Rheumatic Fever: Its Incidence in the Southwestern States. California & West. Med. **59:** 114, 1943.

A report based on a group of 112 proved cases of rheumatic fever studied in private practice, and an analysis of the information and reports on 83 additional cases admitted to one of the private hospitals in San Diego, California, is given. These patients were all children, ranging in age from 3 to 15 years. They were all native of southern California or southwestern Arizona, and had not resided outside that area at any time. The purpose of the study was to determine the type, severity, and season of onset, and the extent of cardiac damage in these patients.

Acute rheumatic fever and rheumatic carditis are found far more frequently in southern California than has been claimed by most observers. The incidence can be charted more accurately if laws requiring reportability of the disease are systematically observed.

The severity of the cardiac complications is approximately as great as in colder and more severe climates. Poor housing and economic conditions do not seem to be contributory factors to the disease in this area. Repeated respiratory and throat infections of a streptococcic type seem to precede the actual onset of the acute attack. The removal of tonsils and adenoids does not seem to alter the incidence of the disease nor act as a prophylaxis.

AUTHOR.

Dressler, M., and Silverman, M.: Cardiovascular Syphilis: An Approach to Early Clinical Recognition and Early Treatment. Ann. Int. Med. **19:** 224, 1943.

Of 1,270 cases of proved syphilis studied, 24 per cent were diagnosed clinically as uncomplicated aortitis, and 30.7 per cent as cardiovascular syphilis as a whole. Of the latter group, 78 per cent were cases of uncomplicated aortitis. The proportion of males to females was approximately two to one, and that of the white to the Negro race approximately the same.

The criteria for the physical diagnosis of uncomplicated aortitis are presented and discussed, and are found of value in patients 40 years of age or younger. It is more common in the Negro than in the white race in this age group.

The high percentage (47.4 per cent) of hypertension among the cases of cardiovascular syphilis studied is not purely coincidental. No valid reason is advanced for its presence.

Uncomplicated aortitis is more common among congenital syphilitics than has been reported before.

Of 128 cases of cardiovascular syphilis that remembered the chancre, uncomplicated aortitis was diagnosed in 38 cases within ten years after the primary infection.

Uncomplicated aortitis is a symptomless disease. Hints on physical diagnosis were discussed.

Neurosyphilis was present in 26.6 per cent of the cases of cardiovascular syphilis. Fluoroscopy and roentgenography are of value in corroborating the clinical diagnosis. Uncomplicated aortitis can be diagnosed clinically in normal-sized aorta.

An outline of treatment is presented.

AUTHORS.

Cooke, W. T., and Cloake, P. C. P.: Extreme Cardiac Hypertrophy: Report of Two Cases With Aortic Hypoplasia and Endocrine Disorders. Brit. Heart J. 5: 139, 1943.

Two cases of extreme cardiac hypertrophy are reported.

In the first, a male diabetic, aged 33 years, the heart weighed 1,350 grams. There was no associated valvular disease and only moderate increase in the size of the heart chambers. The descending part of the thoracic and abdominal aorta showed moderate hypoplasia. No definite cause for this extreme cardiac hypertrophy could be found, but there was evidence of thyrotoxicosis, and it is suggested that pituitary hyperfunction played some part.

In the second, a female acromegalic, aged 35 years, the heart weighed 900 grams. The hypertrophy affected the left ventricle predominantly and was associated with an interauricular septal defect and hypoplasia of the aorta. The pituitary dysfunction was thought to have played the chief part in the production of the enlargement in this case.

AUTHORS.

Pickering, G. W.: The Circulation in Arterial Hypertension. Brit. M. J. 2: 1, 31, 1943.

This article is an abridged version of the Oliver-Sharpey Lectures delivered at the Royal College of Physicians of London, in 1943. It is an important outline and résumé of present knowledge concerning the nature of hypertension and its effect on the circulation in general.

MCCULLOCH.

Foà, P. P., Foà, N. L., and Peet, M. M.: Arteriolar Lesions in Hypertension: A Study of 350 Consecutive Cases Treated Surgically. An Estimation of the Prognostic Value of Muscle Biopsy. J. Clin. Investigation 22: 727, 1943.

The ratio of the thickness of the wall to the diameter of the lumen (W/L) of the arterioles in skeletal muscle was computed from data obtained by direct measurement of the blood vessels in biopsy material. Three hundred and fifty consecutive cases of arterial hypertension were studied. All the patients were subsequently submitted to supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy, and were followed for nine months to seven years after operation. The degree of thickening of the arteriolar wall was compared to the severity of other signs and symptoms and to the therapeutic results. Patients with more severe thickening of the arteriolar wall had more severe symptoms, showed poorer therapeutic results and greater mortality. The correlation is particularly significant between arteriosclerosis and other evidence of damage to the vascular system, such as the elevation of the blood pressure. The results show that the determination of W/L in skeletal muscle adds very significant information to the clinical and pathologic picture of hypertension. It is important in the prognosis of the disease. The results are in agreement with the hypothesis that the surgical treatment of hypertension described here gives better results when hypertension is due to a spasm of the arterioles or to a mild, reversible degree of hypertrophy of the muscle fibers in the

media, and not when severe permanent anatomic lesions have transformed the majority of the arterioles into narrow and rigid tubes.

It is suggested that the study of hypertensive patients should include, whenever possible, the determination of the intensity of the vasomotor reactions, the measurement of the effective renal blood flow by diodrast clearance, the observation of the blood vessels of the eye grounds, and the determination of the wall/lumen ratio of the arterioles in muscle biopsies. This direct investigation of the vascular system is at least as important as the examination of the heart and of the renal function, which reveals the extent of the damage produced by hypertension to vital organs and functions, rather than the severity of the disease itself and the extent to which vascular lesions have become irreversible.

AUTHORS.

Massie, E., and Miller, W. C.: The Heart Size and Pulmonary Findings During Acute Coronary Thrombosis. Am. J. M. Sc. 206: 353, 1943.

The change in heart size in sixteen patients following unequivocal acute coronary thrombosis was studied by teleoroentgenograms taken over periods extending from twelve hours to seven months following the acute attack.

No consistent change in cardiac size or shape was noted in this study. Eight of the patients showed no change in any of their entire series of films. Each of four other patients presented only one film with cardiac measurements significantly different from the others of their respective series, and these were taken at greatly varying intervals (three days to three months) after the attack, with both increasing and decreasing measurements occurring. It is noteworthy that, in the important first two weeks following the acute accident, only four cases of the entire series had a change in cardiac measurements; in two they were increased, and in the other 2 they were decreased.

It is impossible to state from this study that there is any significant feature which characterized the eight patients who showed a change in cardiac size following coronary thrombosis. Nevertheless, the more frequent occurrence of complications within this group attracts attention. Aside from these complications, it appeared that the patients with significant change in cardiac size were somewhat more ill than the others.

The findings in the roentgen ray films of pulmonary congestion in the first and second weeks following the coronary accident were especially noteworthy. Twelve patients showed roentgenologic evidence of such pulmonary involvement, whereas, in only seven of these, did auscultation reveal the presence of basal râles. In four patients, evidence of pulmonary congestion was lacking on both roentgen ray and physical examination.

AUTHORS.

Altschule, M. D., Zamcheck, N., and Iglauer, A.: The Lung Volume and Its Subdivisions in the Upright and Recumbent Positions in Patients With Congestive Failure. Pulmonary Factors in the Genesis of Orthopnea. J. Clin. Investigation 22: 805, 1943.

Studies of the subdivisions of the lung volume were made in twelve patients with congestive failure in the sitting and recumbent positions.

No increase in the degree of pulmonary congestion was demonstrated in recumbency in orthopneic patients.

A cephalad shift of the diaphragm occurs in recumbency; this causes changes in respiration and circulation which tend to increase dyspnea.

The complexity of interrelated factors which are related to the genesis of the orthopnea of congestive failure is discussed.

AUTHORS.

Starr, I.: Clinical Studies on Incoordination of the Circulation as Determined by the Response to Arising. J. Clin. Investigation 22: 813, 1943.

The response of the circulation when the subject arose, as determined by the ballistocardiograph, has been employed as a test of its coordination, i.e., of the ability to adapt the cardiac output to the needs of the moment.

Normal standards for circulatory coordination have been determined by a statistical analysis of the results of 120 tests made on 75 healthy young adults, before and after arising. Over 150 patients have been studied also.

In healthy persons, the physiologic adjustment necessitated by assuming the erect position is largely accomplished by the basomotor mechanism, and the cardiac output changes but little.

In many sick persons, the circulation changes much more, and the abnormality may be in either direction. In the commoner type, the circulation is unduly increased on arising, as if the vasomotor responses were insufficient to support the blood pressure unaided. This type is found with great frequency in many types of disease. In the much rarer type, the circulation abnormally diminishes on arising.

Many weakened patients cannot stand without involuntary muscular movements of the lower extremities. Such movements are always called forth in persons subjecting to fainting before they collapse, and they seemed designed to support the circulation. The authors regard their presence as evidence of the inadequacy of the vasomotor and other circulatory responses to maintain blood pressure.

Patients with symptoms referable to their circulation without detected organic disease, the group often diagnosed as neurocirculatory asthenia, show incoordination of the circulation in a large majority of cases. The frequency of such incoordination in many conditions of disease is suggested as the reason for the widespread occurrence of the symptoms these patients exhibit, such as undue breathlessness on exertion, faintness, dizziness, and the like.

AUTHOR.

Dexter, L., Frank, H. A., Haynes, F. W., and Altschule, M. D.: Traumatic Shock. VI. The Effect of Hemorrhagic Shock on the Concentration of Renin and Hypertensinogen in the Plasma in Unanesthetized Dogs. J. Clin. Investigation 22: 847, 1943.

A study has been made of the renal humoral pressor mechanism, in unanesthetized dogs in shock, from the removal of 4 to 5 per cent of the body weight of blood.

It is confirmed that readily detectable amounts of renin appear in the circulating plasma.

The concentration of hypertensinogen in plasma decreases in severe hemorrhagic shock, sometimes to extremely low levels. Since, in shocked dogs which have been nephrectomized, the concentration of hypertensinogen remained unchanged or increased, it is assumed that its diminution in shocked dogs with intact kidneys is due mainly or solely to the presence of excessive amounts of renin.

Transfusion of 4 to 5 per cent of body weight of whole blood, with nearly normal titer of hypertensinogen, did not increase the concentration of hypertensinogen in plasma appreciably, presumably due to its almost immediate conversion to hypertensin by the large amount of circulating renin.

The renal humoral pressor mechanism is considered to represent a compensatory measure, on the part of the body, to maintain normal blood pressure in dogs rendered hypotensive by hemorrhage.

This mechanism functions inadequately, however, due to the inability of the organism to synthesize hypertensinogen as rapidly as it is converted to hypertensin by the large excess of circulating renin.

AUTHORS.

Steinberg, M. F., Grishman, A., and Sussman, M. L.: Angiocardiography in Congenital Heart Disease. II. Intracardiac Shunts. Am. J. Roentgenol. **49:** 766, 1943.

Sixty-five congenital cardiacs have been subjected to angiocardiography. Eighteen cases represented various types of intracardiac shunts. The method usually demonstrated the shunt when a right-to-left shunt existed and sometimes when it was produced by the injection. In other cases, when the shunt was left-to-right, reopacification of the right heart could be made out occasionally. In all cases, the demonstration of the pathologic anatomy and physiology present was of value in differential diagnosis. It is likely that with additional data better evaluation of prognosis will be possible.

AUTHORS.

Shapiro, R.: "Mitralization" of the Cardiovascular Silhouette in the Posteroanterior Roentgenogram. Am. J. Roentgenol. **50:** 46, 1943.

The term "mitralization," as applied to the cardiovascular silhouette in the posteroanterior roentgenogram, is used to signify a straightening or convexity of the left upper heart border.

The so-called "mitral type" heart may be produced by many different factors or conditions, and is not pathognomonic of a mitral valvular lesion.

The roentgenologic diagnosis of mitral stenosis should not be made from a posteroanterior roentgenogram alone. Oblique views, especially the right anterior oblique view with barium paste in the esophagus, should be taken to demonstrate the presence of left atrial enlargement. The finding of left atrial enlargement tends to favor a diagnosis of mitral valvular disease, although such enlargement may also occur in other cardiac lesions.

The roentgenologist should discard such ambiguous terms as "mitralization," "mitral type heart," "mitral configuration," etc., since they only tend to be confusing and inaccurate.

AUTHORS.

Murray, G.: Aortic Embolectomy. Surg., Gynec. & Obst. **77:** 157, 1943.

A report of five successful aortic embolectomies is given. In all five cases there were no technical difficulties and no accidents or disasters. An extraperitoneal abdominal approach gives a satisfactory exposure through which the operation can be carried out without difficulty. The circulation was restored and the impending gangrene of both legs in each case was immediately replaced by extremities with normal circulation and function. In spite of the fact that most of these cases eventually die of embolism, the patient can be completely relieved of symptoms and return to the original state of health, following surgical treatment of the immediate episode.

AUTHORS.

Haney, H. F., Lindgren, A. J., Karstens, A. I., and Youmans, W. B.: Responses of the Heart to Reflex Activation of the Right and Left Vagus Nerves by the Pressor Compounds, Neosynephrin and Pitressin. Am. J. Physiol. **139:** 675, 1943.

The pressor compounds neosynephrin, pitressin, and angiotonin are capable of producing an inhibition of the heart which is best explained on the basis of reflexes initiated in response to the rise of blood pressure resulting from their vasoconstrictor action. Administration of these pressor compounds may be said to result in a physiologic activation of the vagus nerves.

In experiments on dogs whose right vagus has been cut and whose left vagus remains intact, i.e., left vagus dogs, the response to the pressor compounds commonly includes A-V heart block. Thus, in this group of animals, A-V block followed the injection of neosynephrin in 27 of 37 experiments on fourteen dogs, of pitressin in 7 of 10 experiments on seven dogs, and of angiotonin in a single experiment.

I dogs whose left vagus had been cut and whose right vagus remained intact, i.e., right vagus dogs, no instances of A-V heart block occurred in response to injection of neosynephrin in 28 experiments on twelve dogs, of pitressin in 12 experiments on six dogs, and of angiotonin in a single experiment.

Physiological activation of either the right or the left vagus results in sinus bradycardia. No remarkable difference in the degree of heart slowing produced by the left as compared with the right vagus is evident.

As a result of physiologic activation of the right vagus, the automaticity of the S-A node frequently is depressed to a level at which the A-V node takes over the function of pacemaker. Thus, A-V nodal rhythm was observed in 4 of 28 experiments using neosynephrin, and in 1 of 12 experiments using pitressin. A-V nodal rhythm occurred in none of the experiments involving the left vagus group of dogs.

The completely denervated heart of the dog is not depressed by neosynephrin in the doses in which it was employed.

In the majority of experiments, pitressin fails to cause significant inhibition of the completely denervated heart. When inhibition occurs, it is usually of small degree.

AUTHORS.

Chen, K. K., Elderfield, R. C., Uhle, F. C., and Fried, J.: Synthetic Glycosides of Digitoxigenin, Digoxigenin, and Periplogenin. J. Pharmacol. & Exper. Therap. 77: 401, 1943.

Six synthetic glycosides, namely, digitoxigenin-β-, digitoxigenin-β-tetraacetyl-, digoxigenin-β-, digoxigenin-β- tetraacetyl-, periplogenin-β-, and periplogenin-β- tetra-acetyl-α-glucosides, have been studied pharmacologically and compared with their corresponding natural glycosides and aglycones—digitoxin, digitoxigenin, digoxin, digoxigenin, periplocymarin, and periplogenin.

In cats, digitoxigenin-, digoxigenin-, and periplogenin-β-α-glucosides are more powerful than digitoxin, digoxin, and periplocymarin, respectively. All the tetra-acetyl derivatives have a low potency.

In frogs, the results are less uniform. While digitoxigenin- and digoxigenin-β-α-glucosides are more active than digitoxin and digoxin, respectively, periplogenin-β-α-glucoside is weaker than periplocymarin. There is also suggestion that digoxigenin-β-tetraacetyl-α-glucoside is more active than digoxigenin.

Periplogenin is decidedly less potent than periplocymarin, indicating the favorable influence of the sugar component in the molecule of the glycoside.

AUTHORS.

Finch, C. A., and Marchand, J. F.: Cardiac Arrest by the Action of Potassium. Am. J. M. Sc. 206: 507, 1943.

Two cases of fatal potassium poisoning have been described. In one, there was a spontaneous accumulation of the serum potassium to 8.85 meq./1 and a further elevation to 10.50 after an oral dose of 4.5 Gm. of the chloride. The other had been given large therapeutic doses for five days. In each there was a failure of renal excretion.

The diagnosis was made by comparison of the findings in these cases with those reported in experimental potassium poisoning, including the serum and urine potas-

sium levels (Case 1), the electrocardiogram, and the clinical course. The relationship of paralysis and of renal failure to potassium poisoning was discussed, and the electrocardiographic changes leading to arrest of the heart have been shown and described.

The parallel features of these two cases illustrating the clinical course of human potassium poisoning were the result of the combined effect of the potassium poisoning and the underlying disease. In each there was: (a) an acute uremia with oliguria; (b) recurrent nausea and retching; (c) episodes of bradycardia unaccompanied by symptoms of cardiac failure or changes in blood pressure; (d) a sudden ascending flaccid quadriplegia without paralysis of the trunk or disturbance of speech or mental functions; (e) electrocardiographic changes including elevated T waves, absent P waves, intraventricular block, and terminal irregularities of the rhythm; (f) arrest of the heart in diastole prior to the cessation of respiration.

AUTHORS.

Forster, R. E., II.: The Medical Use of Thiocyanates in the Treatment of Arterial Hypertension. Am. J. M. Sc. 206: 668, 1943.

The majority of clinical workers believe that thiocyanate has a definite hypotensive effect in the arterial hypertensive patient. However, this hypotensive effect has not been demonstrated in the laboratory. The mechanism by which this clinical blood pressure drop occurs is not known. It is to be hoped that a complete statistical analysis will be done in the future to prove this suspected hypotensive effect.

A satisfactory method for the administration of thiocyanate has been suggested by Barker, which will give minimal toxicity if handled correctly. Thiocyanate should never be given without blood levels being taken. Thiocyanate is not a blanket cure-all for "hypertension" and should be used only in selected cases and where no contraindication exists.

Any relief of subjective symptoms bears minimal relation to the blood pressure drop.

AUTHOR.

Book Review

Modificaçoes de Forma do Eletrocardiograma: By Dr. Dante Pazzanese, Chefe das Clinicas Cardiologicas do Hospital Municipal de São Paulo e do Servico Cirurgico do Professor B. Montenegro, Grafica da Prefeitura, São Paulo, 1942, 373 pages, 247 illustrations.

This new book on electrocardiography has distinctive features. Essentially, it is divided into two parts: The first describes the changes in the various electrocardiographic waves; it is, therefore, a theoretical study. The second describes electrocardiographic changes in various diseases, and is, therefore, an applied study with practical aims.

Each chapter has a short introduction; this is followed by a discussion of the tracings, and then by a summary in both Portuguese and English. The book contains a detailed and up-to-date review of the literature. Most of the tracings are original, and they are usually clear and typical.

Some aspects of this book might be considered either virtues or defects, according to the point of view of the reader. The dogmatic and strongly worded expression of personal views and the detailed and laborious quotation of too many authors are among them.

Some chapters, such as that on electrocardiographic changes in infectious and parasitic diseases, and that on acute accidents and "agony of the heart," will be useful for reference, and are more complete than in other, similar books.

The translation of the summaries into English is adequate.

Dr. Pazzanese has written an interesting and valuable book which should have a place in the library of any cardiologist.

Aldo Luisada.

Erratum

In the article entitled "On Certain Applications of Modern Electrocardiographic Theory to the Interpretation of Electrocardiograms Which Indicate Myocardial Disease," by Robert H. Bayley, which appeared in the December, 1943, issue of the Journal, volume 26, page 808, the second sentence in the second paragraph should read: "The vector G is known as the manifest mean electrical axis of QRST, or as the gradient, which may be said to point from regions in the ventricular muscle at the epicardial and endocardial surfaces in which the average duration of the excited state is greatest, toward regions in the muscle at these surfaces where the average duration is least."

American Heart Association, Inc.

1790 Broadway at 58th Street, New York, N. Y.

THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The American Heart Journal is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is $5.00. Journal membership at $11.00 includes a year's subscription to the American Heart Journal (January-December) and annual membership in the Association. The Journal alone is $10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

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*Executive Committee.

American Heart Journal

VOL. 27 APRIL, 1944 No. 4

War Number

EDITORIAL

THE present number of the AMERICAN HEART JOURNAL consists of various papers of cardiovascular interest which have a direct bearing on the war. They include articles on the problems of cardiovascular examination for admission to the Armed Services and also on cardiovascular problems that face medical officers after the men have been inducted and are in training or on combat duty.

The cardiovascular criteria for admission to the Army (Mobilization Regulations 1-9, adopted also for the enlisted personnel of the Navy) are presented at the end of the introduction of the re-examination paper. A discussion of the individual criteria such as blood pressure, pulse rate, heart size, auscultatory findings, electrocardiography, neurocirculatory asthenia, and history of rheumatic fever appears in the re-examination paper and in several of the other articles.

The most important cardiovascular problem in the Army and Navy is that of the rheumatic heart, especially in its acute phase during rheumatic fever. Indications are at hand to show that a personal or family history of past rheumatic fever is of the greatest importance in identifying those individuals most likely to develop rheumatic fever after exposure to the hemolytic streptococcus. The problem of rheumatic fever is widespread but, naturally, more common in certain regions, as has long been known. A discussion of the subject will be found in the article by Dr. Massell and Dr. Jones.

Neurocirculatory asthenia, which, labeled as such, was a great problem in the last war, is under renewed investigation in the present war. It has not been found, or at least diagnosed, in our Armed Forces in this war, either at home or abroad, nearly as often as in the last war. There are probably several reasons for this, among them a change in style of diagnosis whereby more of such cases are called psychoneurosis or anxiety neurosis; but it also seems likely that the more careful neuropsychiatric examination of the inductees and study of the men in training have weeded out a good many cases from the Service who, in other wars, would have been taken in. Also, the tempo of our Army's fighting has not, to date (Jan. 1, 1944), been as extreme as in the last war.

Other cardiovascular problems in active military service have been minimal. It has been encouraging to find relatively few men with chronic heart disease admitted to the Army and Navy. Here and there, to be sure, one discovers cases, especially those with minimal aortic and mitral valve lesions where the diastolic murmurs are sometimes heard with difficulty. By and large, more men suspected of having heart disease but without it have been excluded than those accepted with supposedly normal hearts who really have some heart disease. As noted above, the development of rheumatic heart disease in service is a major problem. Other types of heart disease are found relatively infrequently. These include cardiovascular syphilis, and hypertensive, pulmonary, and coronary heart disease. Some of the older enlisted men and officers are prone naturally to develop evidence of coronary heart disease, either electrocardiographic or symptomatic, including full-blown myocardial infarction. Most of them are retired from service. Relatively unimportant disorders of cardiovascular function, in particular the arrhythmias, are found occasionally and are dealt with individually. Premature beats are of little or no importance, but paroxysmal tachycardia, especially when frequent, is a cause for rejection as noted in MR 1-9, as are also auricular fibrillation, auricular flutter, and heart block.

It is very important to observe that overemphasis of slight variations of the normal electrocardiogram and of the normal x-ray picture of the heart and great vessels has been one of the common errors in the war, especially in the hands of medical officers who have not had extensive experience and training. Many times the electrocardiogram and x-ray picture have proved more misleading than helpful. This, of course, should not be.

Traumatic lesions of the heart and great vessels in warfare are common, of course, and very often fatal; sometimes, however, recovery ensues, with interesting findings, as noted in Dr. Bland's paper. This traumatic type of heart disease naturally increases when the tempo of the war speeds up. Here expert surgical attention at the front is of prime importance and, with the development of thoracic surgery in recent years, many lives are now being saved.

Vascular injuries and disorders have little representation in this number of the JOURNAL, except for a helpful paper on shock, but it is planned and hoped to present papers along this line in a future number.

It is hoped that a number of physicians in military or in civilian service may have contributions of special military interest and importance that they would like to submit to the JOURNAL for publication. Enough additional papers of value may thus accumulate to permit the publication of a second War Number.

Paul D. White

RE-EXAMINATION OF 4,994 MEN REJECTED FOR GENERAL MILITARY SERVICE BECAUSE OF THE DIAGNOSIS OF CARDIOVASCULAR DEFECTS*

Individual Reports by the Chairmen of Special Medical Advisory Boards in Five Cities in Which the Combined Study Was Made

G. K. Fenn, M.D., Chicago, Ill., William J. Kerr, M.D., San Francisco, Calif., Robert L. Levy, M.D., New York, N. Y., William D. Stroud, M.D., Philadelphia, Pa., and Paul D. White, M.D., Boston, Mass.

INTRODUCTION

Robert L. Levy, M.D., William D. Stroud, M.D., and Paul D. White, M.D.

Members of the Subcommittee on Cardiovascular Diseases, National Research Council

OF THE first two million registrants examined for general military service, one million were rejected for all causes. According to an estimate made by the Selective Service System, approximately 10 per cent of the rejectees were disqualified because of cardiovascular diseases. This rate seemed high for men between 18 and 38 years of age. Accordingly, at a meeting of the Subcommittee on Cardiovascular Diseases of the National Research Council, held in Washington on June 27, 1942, a plan was proposed for the re-examination of a relatively large number of men already rejected for defects of the heart and circulation and for neurocirculatory asthenia. It was hoped that such re-examination would yield information of value for future use concerning particular problems in diagnosis, and that it might result in the salvaging of man power.

The proposal was promptly approved by Major Gen. Lewis B. Hershey, Director of the Selective Service System, and was initiated with the help of Col. Leonard G. Rowntree, Chief of the Medical Division. Upon the recommendation of the Committee on Medical Research, the project was sponsored by the Office of Scientific Research and Development. During the early months of 1943, approximately 5,000 rejectees were re-examined in five large cities by medical boards composed of experts in the field of cardiovascular diseases. Boston, Chicago, New York, Philadelphia, and San Francisco were, for various

*The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Pennsylvania; and under the auspices of National Headquarters, Selective Service System, Washington, D. C.

reasons, chosen for the study, of which a combined summary report has already been published.*

The individual city reports, which include additional information and suggestions not incorporated in the combined report, are presented herewith, together with the diagnostic nomenclature employed by all of the examining boards. The use of a standard list of diagnoses especially adapted for this work made it possible to prepare uniform tables of results. The standards of physical examination (MR 1-9) used at the time of this study are appended to this introduction.

The reader is referred to the combined report for full discussion; but, for convenience, the summary and conclusions are here republished:

1. An analysis has been made this year of the re-examination, by physicians trained in the study of cardiovascular diseases, of 4,994 men rejected for military service by local boards and induction stations because of the diagnosis of cardiovascular defects or neurocirculatory asthenia. The project was carried out under the auspices of the Selective Service System and with the aid of support from the Office of Scientific Research and Development. The registrants were composed of groups of approximately 1,000 men each, in five cities: Boston, Chicago, New York, Philadelphia, and San Francisco.

2. The chief reasons for the re-examination were to determine (a) the problems in cardiovascular diagnosis that particularly concern the range of the normal cardiovascular system with respect to service, (b) the possible salvage of men for the Army by reclassification as 1A, and (c) the comparison of opinions of cardiovascular experts with those of the examiners at local boards and induction stations to determine the desirability of such re-examinations in this or other special medical fields throughout the country.

3. Of the total number of 4,994 cardiovascular rejectees examined, there were 863 (17.3 per cent) resubmitted as 1A, and 4,131 (82.7 per cent) whose rejection as 4F was confirmed.

4. The percentage of men resubmitted as 1A was quite similar in Boston (18.8 per cent),† New York (19.2 per cent), and Philadelphia (16.5 per cent). In San Francisco 28.6 per cent were resubmitted.‡ Chicago yielded the lowest salvage (3.8 per cent), apparently because of the fact that cardiovascular experts had already been freely used in the decision about doubtful cases, a procedure which might profitably be followed by other examining groups throughout the country.

5. The chief cause for rejection was rheumatic heart disease, found in 2,476 men, or 50 per cent of the total 4,994 and 59.9 per cent of the final 4F group. Mitral valvular disease without aortic valvular disease was diagnosed in the majority of these rheumatic heart cases.

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*Levy, R. L., Stroud, W. D., and White, P. D.: Report of Reexamination of 4,994 Men Disqualified for General Military Service Because of the Diagnosis of Cardiovascular Defects, J. A. M. A. 123: 937, 1025, 1943.

†Another 11.4 per cent were considered "borderline" in Boston but after special consideration were not resubmitted.

‡The men resubmitted in San Francisco included a moderate number of "borderline" cases, but in Chicago, New York, and Philadelphia the majority of "borderline" cases were rejected again.

1,500, or 60.6 per cent (750 with obvious stenosis); aortic valvular disease without apparent mitral valve involvement in 280, or 11.3 per cent (72 aortic stenosis and 208 aortic regurgitation alone); and mitral and aortic valvular disease combined in the remaining 628, or 25.4 per cent. Auricular fibrillation complicating mitral stenosis was found in 24 of the cases. The incidence of rheumatic heart disease varied from 70.3 per cent of the rejectees in Chicago to 39.6 per cent in San Francisco.

6. The second most common cause for final rejection was hypertension, found in 1,059 men (25.6 per cent of the 4F group and 21 per cent of the total series). The majority showed elevation of both systolic and diastolic levels; a few had either systolic hypertension alone or diastolic hypertension alone. The incidence varied little from city to city, but it was relatively more common in the fourth than in the third decade.

7. Third in frequency as a cause of rejection was neurocirculatory asthenia with 204 cases (4 per cent of the total series, or 4.9 per cent of those finally labeled 4F). Negroes were rarely affected. The incidence varied from 78 (7.8 per cent) in Boston to 11 (1.1 per cent) in Chicago.

8. The fourth condition responsible for rejection of more than 100 men was sinus tachycardia; there were 189 cases, or 3.8 per cent of the entire group and 4.6 per cent of the final 4F group. The numbers varied from 75 in Chicago to 8 in Philadelphia.

9. The fifth most common cause for rejection was congenital heart disease, found in 183 men (4.4 per cent of the 4F group). The abnormality most commonly diagnosed was ventricular septal defect (Roger's disease) in more than a third of all the cases, 73. Five other defects, in the order of their frequency, were: patency of the ductus arteriosus (29 cases), pulmonary stenosis (13 cases and 2 more with the tetralogy of Fallot), coarctation of the aorta (14 cases), auricular septal defect (6 cases), and subaortic stenosis (5 cases). The city incidence varied from over 6 per cent (63 cases) in San Francisco to 1.8 per cent (18 cases) in Philadelphia.

10. Other causes for rejection included cardiac enlargement alone, determined by x-ray examination (76 cases), arrhythmia in 32, including 17 cases of paroxysmal tachycardia, 6 of uncomplicated auricular fibrillation, 2 of auricular flutter, and 5 of auriculoventricular block, electrocardiographic abnormalities alone in another 32 cases including 10 with bundle branch block, cardiovascular syphilis in only 17 cases, thyrotoxicosis in 14, recent rheumatic fever in 13, cardiac strain from chest deformities in 10, coronary heart disease in only 6, pericarditis in 4, and peripheral vascular defects in 3. Unspecified heart disease was diagnosed in 113 cases.

11. A history of rheumatic fever was obtained in slightly over a fourth of all the cases of rheumatic heart disease (28.8 per cent in

four of the cities) and in nearly half of those in Boston and New York. A history of chorea was rare (1.8 per cent of the rheumatic heart cases in these same four cities).

12. Although the great majority re-examined were white men, there were a good many Negroes (something under 10 per cent, 386 out of 4,035 examined in four of the five cities) and a few Chinese and Filipinos. There was a high rejection rate for Negroes (88 per cent) and a very high rejection rate for the Chinese and Filipinos (100 per cent) in the four cities in which racial data were obtainable. Nine of the fifteen cases of aortic syphilis found in those cities were among Negroes, and hypertension was also more often found in the Negroes (38.5 per cent of the final 4F cases compared to 23.1 per cent for the white men). Rheumatic heart disease was evenly represented (63.8 per cent compared to 63.9 per cent), but neurocirculatory asthenia was very much less common in the Negroes (0.9 per cent compared to 5.5 per cent).

13. There were eight problems of particular interest which remain unsolved and should be the focus of follow-up study but concerning which tentative opinions were expressed: (a) the interpretation of apical systolic murmurs (may they, if very slight or even slight, in the absence of any other abnormal or doubtful finding, be considered inadequate reason for rejection?); (b) the upper limits of the normal blood pressure (may the systolic pressure in very nervous young men be set perhaps as high as 160 mm. Hg or even a shade more, provided the diastolic pressure does not exceed 90 mm. Hg?); (c) the limits of the normal pulse rate at rest (may there not be a wider range, say from 40 to 120 per minute, than that actually given in the current criteria?); (d) the heart size, which also varies widely, especially according to body build, and may perhaps in a few normal individuals exceed the standards set by Hodges and Eyster; (e) the electrocardiogram, of which the wide range of normal has not yet been explored adequately; (f) neurocirculatory asthenia, difficult to diagnose in mild degree, but probably rejectable even when slight, unless there is an obvious cause which can be corrected; (g) recent rheumatic fever, a hazard even when the heart seems perfectly normal; and (h) exercise tests, the usefulness of which, in cardiovascular examination for military service, is open to question.

14. A follow-up study of the men reclassified as 1A and especially of the doubtful "borderline" cases in the final 4F group should, in the years to come, aid in solving some of the various problems in cardiovascular diagnosis that still remain.

15. The wisdom of extending these re-examinations for the sake of the salvage alone is doubtful in view of the time required, the few expert examiners available, and the relatively small percentage of men reclassified as 1A; but the applications of the lessons learned in the course of this study should be helpful in future examinations.

Diagnostic Nomenclature of Cardiovascular Diseases Used by Special Medical Advisory Boards

No cardiovascular disease

Etiologic Type

Bacterial endocarditis—acute
Bacterial endocarditis—subacute
Congenital heart disease (specify lesion if possible)
Coronary heart disease
Hypertension, arterial
Hypotension, orthostatic
Neurocirculatory asthenia
Pulmonary heart disease
Rheumatic heart disease
Syphilitic aortitis

Structural Abnormalities

ENDOCARDIAL

Valvular heart disease—mitral regurgitation—rheumatic
Valvular heart disease—mitral regurgitation—etiology not stated
Valvular heart disease—mitral stenosis, with or without regurgitation
Valvular heart disease—mitral stenosis and auricular fibrillation
Valvular heart disease—aortic regurgitation—rheumatic
Valvular heart disease—aortic regurgitation—syphilitic
Valvular heart disease—aortic regurgitation—etiology not stated
Valvular heart disease—aortic stenosis
Valvular heart disease—combined mitral and aortic disease

MYOCARDIAL

Enlargement of heart (hypertrophy or dilatation, or both)
Enlargement of heart and mitral regurgitation
Myocardial infarction
Myocardial insufficiency (congestive heart failure)

PERICARDIAL

Pericarditis—acute
Pericarditis—chronic

VASCULAR

Aneurysm of aorta
Aneurysm—other than of aorta
Arteriosclerosis
Arteriovenous anastomosis
Lymphedema
Thromboangiitis obliterans
Thrombophlebitis
Other vascular diseases, such as periarteritis nodosa, scleroderma disseminatus, lupus erythematosus disseminatus (specify disease)

Disorders of Function

Adams-Stokes syndrome
Anginal syndrome
Auricular fibrillation
Auricular flutter
Auriculoventricular heart block
Bundle branch block
Carotid sinus syndrome
Paroxysmal tachycardia
Premature beats (extrasystoles)
Raynaud's syndrome (including Raynaud's disease and traumatic vasospastic disease)
Tachycardia (other than paroxysmal)

Mobilization Regulations
No. 1-9

Washington, Oct. 15, 1942
War Department

STANDARDS OF PHYSICAL EXAMINATION DURING MOBILIZATION

Section XIV

Heart, Blood Vessels, and Circulation

62. General service.—a. A heart will be considered normal when the apex impulse is within the left midclavicular line and not below the fifth interspace; when sounds are normal and there are no thrills or important murmurs; when there is no abnormal pulsation or dullness above the base of the heart; when pulse rate is normal and regular and there is no unusual thickening of the arteries or significant elevation of blood pressure.

b. A pulse rate of 100 or over which is not persistent and not due to paroxysmal tachycardia. (A pulse rate of 100 or over may be temporary and due to excitement or to recent infection, such as pneumonia or local infections about the nose, mouth, and throat, or may be induced by drugs.)

c. A pulse rate of 50 or under which is proved to be the natural pulse rate of the individual or to be temporary or due to the use of drugs. (If the bradycardia is physiological, the rate on exercise will rise to a higher level and then gradually return to the original slow rate; whereas, when heart block is present, the rate on exercise will either change slightly or not at all, or sudden interruptions in the length of the heart cycle will be detected.)

d. Sinus arrhythmia. (This consists in a quickening of the pulse rate during inspiration and a slowing during expiration and is best recognized with the individual recumbent and breathing deeply.)

e. Elevation of blood pressure from excitement, proved to be temporary.

f. Neurocirculatory asthenia, if very mild in degree.

63. Limited service.—There are no cardiovascular criteria to warrant initial selection for limited service.

64. Nonacceptable.—a. Circulatory failure evidenced by definite symptoms such as undue breathlessness, pain, or evidence of congestive failure (engorged neck veins, enlarged liver, edema, as well as dyspnea).

b. Hypertrophy and/or dilatation of the heart evidenced by displacement of the apex impulse to the left of the midclavicular line or below the sixth rib, and of a heaving or diffuse character, or by x-ray evidence.

c. A persistent heart rate of 100 or over when this is proved to be persistent in the recumbent posture and on observation and re-examination over a sufficient period of time. See also Section XXI.

d. Paroxysmal tachycardia. See also Section XXI.

e. Heart block.

f. Any serious disturbance of rhythm such as auricular fibrillation.

g. Valvular disease.

h. Congenital heart disease.

i. Persistent blood pressure at rest above 150 mm. systolic or above 90 diastolic, unless in the opinion of the medical examiner the increased blood pressure is due to psychic reaction and not secondary to renal or other systemic disease.

j. Thrombophlebitis of one or more extremities if there is a persistence of the thrombus or any evidence of circulatory obstruction in the involved vein or veins.

k. Other abnormalities of the peripheral vascular system, including large varicose veins, Raynaud's disease, Buerger's disease (thromboangiitis obliterans), erythromelalgia and arteriosclerosis. In doubtful cases special tests should be employed.

l. Aneurysm of any vessel.

m. Pericarditis.

n. Acute endocarditis.

o. True angina pectoris.

p. Coronary thrombosis.

q. Neurocirculatory asthenia (effort syndrome), unless very mild. Usual symptoms of this condition are exhaustion, breathlessness, heartache, and palpitation. These symptoms may follow exertion such as would not produce them in healthy individuals. These and other symptoms, such as dizziness or fainting, may arise without evidence of organic disease sufficient to account for the disability of the individual. Cases of effort syndrome may be divided into four groups. (In some cases more than one of these factors is present.)

(1) As an accompaniment of organic heart disease.

(2) Following infections.

(3) In individuals with poor physique or insufficient training for the work required.

(4) Orthostatic hypotension or tachycardia.—The blood pressure and pulse rate will be taken with the individual in the recumbent position and after standing three minutes. An increase in a normal recumbent pulse rate of 120 beats per minute or more when the individual stands, or a decrease of a normal blood pressure (when the individual is recumbent) to values less than 90 systolic and 60 diastolic when the individual stands may be considered evidence of a definite physiologic disturbance and in itself cause for rejection unless the condition is very temporary following an illness, operation, or exhausted state.

65. Electrocardiogram.—The electrocardiogram is of great assistance in determining the nature of certain cardiac abnormalities, the most important of which are the various arrhythmias, defects in conduction, and diseases of the coronary arteries. The electrocardiograph may be utilized in cases where such diagnostic aid is especially indicated but will not be employed as a routine measure.

66. X-ray.—In doubtful cases, fluoroscopy and teleoroentgenography are advised to determine the size and shape of heart and great vessels. Films taken for the study of the lungs will also be viewed for cardiovascular defects.

REPORT OF THE BOSTON BOARD

PAUL D. WHITE, M.D., CHAIRMAN

THE following pages contain a summary of the re-examination of 1,000 men rejected for military service for cardiovascular reasons or neurocirculatory asthenia by the Boston local boards and Induction Station between the years 1940 and 1943. The re-examinations were carried out by a Medical Advisory Board (No. 16) consisting of the physicians listed below, with the help of secretaries, technicians, and volunteer aides, also listed below. The examinations were conducted at the Massachusetts General Hospital, on Tuesday and Thursday evenings and Saturday afternoons beginning February 4 and ending March 18, each session lasting three to four hours, during which time between 40 and 70 men were thoroughly examined and graded as either 4F, that is, with rejection confirmed, or 1A conservative, that is, with recommendation of acceptance for military service according to the strict interpretation of MR 1-9, or "1A liberal," which group included borderline cases, the criteria for which will be outlined below. All those men recommended as 1A conservative and borderline ("1A liberal") had electrocardiograms taken and were studied roentgenologically. A few other laboratory tests were carried out.

The routine examinations were made, after measuring and weighing the men, in the booths of the Metabolism Laboratory at the Massachusetts General Hospital, by five teams of physicians. For special examination purposes and for resting the men whose blood pressures or pulse rates were too high, small quiet rooms were available in the Cardiac Laboratory. The usual method of examination of the heart was carried out with the individual recumbent and, if necessary, after exercise, using two stethoscopic chest pieces, the Bowles and the bell, and the mercurial sphygmomanometer. The murmurs were graded according to Dr. Levine's classification of: (1) very slight, (2) slight, (3) moderate, (4) loud, (5) very loud, and (6) with murmur heard with chest piece or ear off the chest. Frequent consultations were held between the different teams on special cases and always at least two of the senior examiners agreed on the classification of the men graded 1A conservative and borderline ("1A liberal"). Frequently, all nine examiners were called to conferences during the examining sessions to discuss general principles, special cases, and moot points. One of the examiners, Dr. Cohen, a neuropsychiatrist with cardiovascular training was available for psychiatric consultation.

It was agreed that the men designated as 1A conservative should be sent up some time in the spring by the local boards to the Boston Induction Station for reconsideration, provided they were still liable

for military service. The men designated borderline ("1A liberal") are to be classed temporarily along with those labeled 4F as unsuitable for military service, but because of the importance of this group, a follow-up will be carefully arranged for the future as well as a follow-up of the men in group 1A conservative, whether they have been inducted into the Army or not. Arrangements were made to send the serial numbers of those inducted to Colonel Victor D. Washburn and to the Special Medical Advisory Board, Dr. Paul D. White, Chairman, for the purpose of future follow-up. Copies of the records of all the cases of 4F, 1A conservative, and borderline ("1A liberal"), on the form used, a sample of which is appended, have been retained by Colonel Washburn of the Massachusetts Selective Service and by Dr. Paul D. White.

The examinations went off especially well due to the close cooperation of all those involved, including the examinees, and especially because of the untiring and devoted help of Colonel Victor D. Washburn, Medical officer of the Selective Service in Massachusetts. There was only one untoward event, the sudden death of one of the men previously rejected for rheumatic heart disease, while he was seated waiting for his turn in the examination on Saturday afternoon, March 13. Investigation revealed the fact that this man had been seriously ill with rheumatic heart disease and heart failure a few months before, but had recovered, had recently married, and had been in fair, though probably a mediocre, state of health just prior to his visit to the hospital. He had been ambulatory for weeks and had been doing light work.

MAKEUP OF TEAMS

Team 1.—Dr. Norman H. Boyer and Dr. James Currens.
Team 2.—Dr. Laurence Ellis and Dr. Currens.
Team 3.—Dr. Burton E. Hamilton and Dr. Conger Williams.
Team 4.—Dr. Samuel A. Levine and Dr. Elwyn Evans.
Team 5.—Dr. Paul D. White and Dr. Mandel E. Cohen.

With the constant help of Colonel Victor D. Washburn,
State Medical Officer, Selective Service, Massachusetts.

Secretaries

Miss Helen Donovan
Miss Louise Wheeler

Technicians

Miss Deborah Hanson
Mr. James Sherlock
Miss Ellen Wood

Aides

Mrs. Edward F. Bland
Mrs. James H. Currens
Miss Edith Terry
Mrs. Robert Vickery
Mrs. Paul D. White
Mrs. Conger Williams

Special Examinations

Electrocardiograms	375
X-rays	337
Blood tests	2
Urinalysis	9
Metabolism tests	2

CRITERIA FOR 1A CONSERVATIVE AND BORDERLINE

The criteria for classification of the men as 1A conservative and borderline in Boston were briefly as follows:

1. *Murmurs.**—A. Apical.—Individuals with apical murmurs of grade 1 (very slight), with no history of rheumatic fever and no evidence of heart disease, were included in the group 1A conservative. If there was a doubtful or unauthenticated history of rheumatic fever, the classification was borderline unless the very slight murmur was inconstant. If there was a clearcut history, authenticated from hospital or private records, of rheumatic fever in such individuals with apical systolic murmurs, they were classified 4F.

If an apical systolic murmur was of the grade 1+ to 2–, that is, between very slight and slight, the classification was borderline if there was no evidence of heart disease otherwise, and no history of rheumatic fever. If there was a *late* systolic murmur of grade 2, the classification was also borderline.

If an apical systolic murmur was of grade 2 or louder, that is, slight to moderate or loud, rejection was in order unless the murmur was completely dispelled in certain phases of respiration (rare for this loudness of murmur).

B. Aortic Area.—A localized systolic murmur at the aortic area of any intensity, unless extremely slight (grade 1–) and dispelled by respiration, was a cause for rejection.

C. Pulmonary Valve Area.—Systolic murmurs of grades 1 and 2 in the pulmonary area were not a cause for rejection if there was no evidence of heart disease. With full expiration a physiologic murmur might reach close to grade 3 in intensity, but it almost always disappeared on full inspiration. A persistent systolic murmur of grade 3 or more in the pulmonary valve area was considered cause for rejection.

D. Left Sternal Border.—A localized systolic murmur more than slight (grade 2–) at the left sternal border unless dispelled by full inspiration was considered cause for rejection.

E. Diastolic Murmurs.—Any diastolic murmur was a cause for rejection. There were, however, a few cases of slight scratchy to-and-fro murmurs, evidently extracardiac and varying with respiration, which we considered physiologic.

2. *Heart Rate.*—A. A pulse rate of 100 or under, before or after resting, was essential for inclusion in group 1A conservative.

B. Heart rates up to and including 120, if thought to be the result of nervous excitement, in the absence of any evidence of heart disease or infection or thyrotoxicosis, were classified as borderline.

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*Suspicion of cardiac thrills without important heart murmurs should be disregarded. (See Dr. Levine's letter on page 453.)

3. *Blood Pressure* (Average of all readings, systolic and diastolic after 30 minutes rest, were taken as final).—A. Maximum systolic and diastolic pressures of 150 mm. and 90 mm. respectively were required for admission to group 1A conservative.

B. Maximum blood pressures of 170 systolic (if the diastolic pressure was not over 90) and 95 diastolic were permissible for inclusion in the borderline group.

4. *Neurocirculatory Asthenia.*—A diagnosis of neurocirculatory asthenia even of slight or very slight degree was a cause for rejection. The diagnosis was dependent on symptomatology and not on instability of pulse rate or blood pressure, which, however, may be corroborative.

5. *Electrocardiogram.*—A. QRS waves measuring over 0.10 second were a cause for rejection. Those which measured 0.10 second or less were acceptable despite prominence of S waves or unusual shape otherwise. They doubtless are within the range of normal.

B. A P-R interval of 0.20 second was acceptable. Although it is possible that a P-R interval of 0.21 or 0.22 second may be within the range of normal, we have not included such cases in 1A, even under liberal classification.

C. Flattening and inversion of the T waves in Leads I and IV were causes for rejection. Flattening or slight notching of the T waves in Lead II, corrected by change in position of the body or the diaphragm, were within the range of normal provided there was no evidence of heart disease otherwise, and so were acceptable.

6. *X-ray.*—Transverse diameter of the heart shadow by 7 foot film not over 1 cm. above the expected normal for the individual's height, weight, and age, according to the Hodges-Eyster formula by slide rule or nomogram, was acceptable for classification in group 1A conservative. Transverse diameters with measurements up to 2 cm. above the expected normal for the individual's height, weight, and age, were on occasion acceptable for classification as borderline provided there was no evidence of heart disease and *provided* the build of the individual was unusual with wide chest and short stature, usually stocky in addition.

Prominence of the left upper border of the heart and of the pulmonary artery, unless excessive, were not bars to acceptance of the individual in classification 1A conservative provided there was no evidence of heart disease otherwise, and especially if the individual had a vertical heart position.

7. *Rheumatic Fever.*—A history of rheumatic fever prior to five years before examination with the absence of any evidence of heart disease did not bar a candidate from military service. Repeated attacks of rheumatism or rheumatic fever within the last five years, and at any date in the presence of evidence of cardiac abnormality, on the other hand, was cause for rejection. Such history was authenticated.

TABLES SHOWING THE RESULTS OF THE BOSTON RE-EXAMINATION

Table I

Re-examination of Cardiovascular Rejectees in Boston During February and March, and on June 8, 1943

	TOTAL	4F	%	BORDER-LINE	%	1A CONSERVATIVE	%
Team 1	186	131	70.5	17	9	38	20.5
Team 2	175	127	73	11	6	37	21
Team 3	219	146	67	38	17	35	16
Team 4	191	141	74	23	12	27	14
Team 5	229	153	67	25	11	51	22
Grand Total	1000	698	69.8	114	11.4	188	18.8

1A Conservative and Borderline ("1A Liberal") = 302 (30.2 per cent)
4F and Borderline ("1A Liberal") 812 (81.2 per cent)

Table II

4F
(Total—698 Cases)

OUR FINAL DIAGNOSIS	TEAM 1	TEAM 2	TEAM 3	TEAM 4	TEAM 5		TOTALS
Rheumatic heart	86	73	80	74	83		396
Mitral							
Stenosis	15	18	15	22	31	101	
Regurgitation alone	14	6	10	12	14	56	
Aortic							
Stenosis	2	6	4	1	5	18	
Regurgitation alone	8	16	19	5	5	53	
Both mitral and aortic	42	24	31	33	28	158	
Without specification	5	3	1	1	0	10	
(With auricular fibrillation)	(0	3	3	1	6	13)	
Arterial hypertension	25	25	34	38	39		161
Systolic alone	0	0	0	4	6	10	
Diastolic alone	7	5	4	5	2	23	
Systolic and diastolic	18	20	30	29	31	128	
Neurocirculatory asthenia	8	13	12	12	16		61
Congenital*	2	11	14	8	8		43
Coronary heart disease	0	0	0	1	0		1
Heart disease unspecified	5	2	0	0	4		11
Recurrent or recurrent rheumatic fever	0	0	1	4	1		6
Paroxysmal tachycardia	2	0	0	1	0		3
Tachycardia	0	1	0	0	1		2
Auricular fibrillation (2) or flutter (1) without other defects	1	0	1	1	0		3
ECG abnormality*	0	1	0	1	1		3
Special*	2	1	4	1	0		8
Totals	131	127	146	141	153		698

*See Table III.

Table III

Congenital Heart Disease	TEAM 1	TEAM 2	TEAM 3	TEAM 4	TEAM 5	TOTAL
Interventricular septal defect	2	5	6	3	5	21
Interauricular septal defect	0	1	2	2	0	5
Subaortic stenosis	0	2	0	0	2	4
Coarctation of aorta	0	2	1	0	0	3
Pulmonary stenosis	0	0	2	0	1	3
Patent ductus arteriosus	0	0	1	1	0	2
Tetralogy of Fallot	0	0	1	0	0	1
Low aorto-pulmonary artery communication	0	0	0	1	0	1
Prominent pulmonary artery	0	0	0	1	0	1
Unspecified	0	1	1	0	0	2
	2	11	14	8	8	43

ECG Abnormalities (3 cases)	
Wide QRS waves (0.11 second)	2
Abnormally long Q-T interval	1

Special (8 cases)	
Chest deformity	2
Thyrotoxicosis	1
Aortic stenosis (? type)	1
Cardiac enlargement (? cause)	1
Albuminuria (persistent)	1
A-V fistula (lung)	1
Cardiac neurosis	1

Table IV

1A Conservative

(Total—188 Cases)

DIAGNOSIS AT TIME OF ORIGINAL REJECTION NOT CONFIRMED BY US	TEAM 1	TEAM 2	TEAM 3	TEAM 4	TEAM 5	TOTALS
Rheumatic heart	20	13	16	11	19	79
Mitral						
Stenosis	1	2	1	1	6	11
Regurgitation alone	17	7	8	7	4	43
Aortic						
Stenosis	2	0	1	0	1	4
Regurgitation alone	0	1	0	0	2	3
Both mitral and aortic	0	0	1	0	0	1
Without specification	0	3	5	3	6	17
Arterial hypertension	9	14	5	8	16	52
Neurocirculatory asthenia	2	4	1	3	7	17
Congenital	0	2	0	1	2	5
Heart disease unspecified	5	3	10	3	6	27
Recent or recurrent rheumatic fever	0	1	2	0	0	3
Heart block	0	0	0	0	1	1
Tachycardia	0	0	1	1	0	2
Extrasystoles	1	0	0	0	0	1
Angina pectoris	1	0	0	0	0	1
Totals	38	37	35	27	51	188

TABLE V

BORDERLINE ("1A LIBERAL")

(Total—114 Cases)

DIAGNOSIS AT TIME OF ORIGINAL REJECTION (NOT CONFIRMED BY US)	TEAM 1	TEAM 2	TEAM 3	TEAM 4	TEAM 5	TOTALS	POSSIBLE OR QUESTIONABLE BUT NOT PROBABLE DIAGNOSES AS FINALLY ASSESSED BY US
Rheumatic heart	7	2	12	5	4	30	19
Mitral							
Stenosis	0	0	2	4	2	8	0
Regurgitation alone	3	0	6	0	1	10	15
Aortic							
Stenosis	0	0	0	0	0	0	0
Regurgitation alone	0	2	0	0	0	2	1
Both mitral and aortic	1	0	0	0	0	1	3
Without specification	3	0	4	1	1	9	0
Arterial hypertension	5	6	14	8	13	46	70
Neurocirculatory asthenia	0	1	5	5	4	15	2
Congenital	1	0	1	0	1	3	2
Heart disease unspecified	4	2	3	3	0	12	1
Enlargement only							10
Tachycardia	0	0	2	2	2	6	27
ECG abnormality only							2
Other (including unstable cardiovascular system)	0	0	1	0	1	2	0
Totals	17	11	38	23	25	114	114+ 19 with combined diagnoses

ADDITIONAL DATA OF INTEREST

There were a number of other interesting relationships noted on analysis of the records, the more important of which are as follows:

a. Among the 23 Negroes examined, 18 were rejected, 4 were classed as borderline, and 1 was passed. Of the 18, 9 were rejected because of hypertension. There was one man of Chinese origin in the total group; he was rejected.

b. There was nothing of particular interest so far as we could make out in the relationship of the place of residence, city or suburbs, of the place of rejection, local board or Induction Station, or of the year of rejection, and the particular conditions found. The majority of the men examined lived in the city and were rejected in 1942 by the Induction Station. It was true, as would be expected, that there was a larger salvage among the cases rejected by the local boards than in those rejected by the Induction Station.

c. Rheumatic heart disease as a confirmed cause for rejection was found much more commonly in the third decade than in the fourth; this was true also, though less strikingly, for neurocirculatory asthenia, but rejection for hypertension was the other way around.

Age Groupings of Rheumatic, Hypertensive, and NCA Cases

	Rheumatic Heart Disease		Hypertension		Neurocirculatory Asthenia	
	Decades		Decades		Decades	
	3rd	4th	3rd	4th	3rd	4th
Team 1	60	26	4	21	5	3
Team 2	58	15	4	21	11	2
Team 3	59	21	10	24	7	5
Team 4	58	16	14	24	6	6
Team 5	63	20	10	29	15	1
	298	98	42	119	44	17

Age Groupings of All Cases

	4F		1A Conservative		Borderline		Total	
	Decades		Decades		Decades		Decades	
	3rd	4th	3rd	4th	3rd	4th	3rd	4th
No.	451	247	124	64	72	42	647	353
							(1,000)	

d. A history of previous rheumatic fever in the 4F cases of rheumatic heart disease was obtained as follows:

Total cases of rheumatic heart disease	396
Definite history of rheumatic fever	185 (47 per cent)
Questionable history of rheumatic fever	10 (2 per cent)

e. One of the most interesting of all the findings was that of the great diversity of the electrocardiograms among the men who otherwise seemed to be absolutely normal. The range of the normal electrocardiogram is certainly wider than had been previously thought.*

It was noted that among the 1A group, S waves were frequently quite prominent in Leads I and II, either in width or depth, without increase in the duration of the QRS waves. Also, there were some interesting variations in the S-T segments and T waves which at first glance rendered one suspicious; everything else, however, was normal.

CHANGES IN DIAGNOSIS BESIDES THOSE TRANSFERRED FROM 4F TO 1A

The most important change in diagnosis, of course, was in all the cases listed on the previous pages as 1A conservative and in many listed as borderline ("1A liberal"). However, there were, in addition, a considerable number of interesting and important changes in diagnosis in the 4F group, men who were confirmed as 4F but not always for the same reasons. Thus, among the 153 4F cases of Team 5, the original diagnosis was considered incorrect in 21, and, less important, it was considered incomplete in 52 others. Examples of incorrect diagnoses were:

1. Heart disease (wrong) for neurocirculatory asthenia (correct) (6 cases).
2. Neurocirculatory asthenia for tachycardia.

*This has been found also among 1,500 normal aviators, reports of which are published in this issue of the American Heart Journal.

3. Rheumatic heart disease for congenital heart disease.
4. Rheumatic heart disease for arterial hypertension.
5. Mitral regurgitation for mitral stenosis.
6. Aortic stenosis for aortic regurgitation.
7. Pericarditis with effusion for rheumatic mitral stenosis with auricular fibrillation and very large heart.
8. Patent ductus arteriosus for ventricular septal defect.

In a number of cases with incomplete diagnoses, defects of one valve and not of the other which was also involved were noted; for example, mitral stenosis might be diagnosed and aortic regurgitation omitted, or vice versa, and, frequently, rheumatic heart disease alone was diagnosed. These were not considered especially important. Though incomplete, they were partial diagnoses, quite likely in an effort to save time, and so were adequate for rejection.

Some errors were encountered by the other teams which need not be rehearsed here, although the details can be found in the original records.

SUMMARY

1. A detailed re-examination of 1,009 cardiovascular rejectees for military service was made in Boston during the months of February and March, 1943. Twelve cases with noncardiac causes for rejection were omitted, leaving 997 cases for the statistical analysis; in order to raise the total to exactly 1,000, six more men were re-examined on June 8 and the first three of these added to the original 997. Nine physicians experienced in cardiovascular examination, including one who had also had extensive neuropsychiatric training, participated. These included Drs. Norman Boyer, Mandel Cohen, James Currens, Laurence Ellis, Elwyn Evans, Burton Hamilton, Samuel A. Levine, Paul D. White, and Conger Williams.

2. Of this number of 1,000 examinees, 69.8 per cent were confirmed as 4F (completely unsuited for military service), 18.8 per cent were recommended as 1A conservative (completely suitable for military service), and 11.4 per cent as borderline ("1A liberal") cases. It is this borderline group, as well as the 1A conservative group, that should be of much interest for future follow-up, although for various reasons we have not recommended that this borderline group be admitted into military service at the present time. Thus, about 19 per cent were considered as salvageable on the basis of their physical condition, with the probability of a total of about 30 per cent (18.8 plus 11.4) falling within the normal range.

3. Among the individuals designated as 4F, the most common confirmed cause for rejection was rheumatic heart disease, making up 39.6 per cent of the total series, or 56.8 per cent of the 4F group. The second most common cause for rejection was arterial hypertension, making up 16.1 per cent of the total, or 24.4 per cent of the 4F group. The third most common cause was neurocirculatory asthenia, comprising 6.1 per cent of the total, or 8.7 per cent of the 4F group. The fourth most

common cause was congenital heart disease, which comprised 4.3 per cent of the total, or 6.2 per cent of the 4F group. The other miscellaneous causes altogether made up only 40 cases, or 5.7 per cent. Miscellaneous cases included recent or recurrent rheumatic fever, paroxysmal tachycardia, uncomplicated auricular fibrillation or flutter, and coronary heart disease (see tables).

4. Of the rheumatic heart cases, mitral valve disease was diagnosed in 315, that is, in the great majority, being associated with aortic valve disease in 158. Mitral stenosis without aortic valve disease was diagnosed in 101 cases, and mitral regurgitation alone in 56 cases. Aortic stenosis without mitral valve disease was diagnosed in 18 cases, and aortic regurgitation alone in 53 cases. Both mitral and aortic valve disease were diagnosed in 158 cases. Rheumatic heart disease without specification was diagnosed in 10 other cases. In 13 of the rheumatic cases, auricular fibrillation complicated the picture, always associated with mitral valve disease.

5. The majority of the cases of arterial hypertension had both systolic and diastolic hypertension, 128 out of 161 cases. Ten had systolic hypertension alone, and 23 had diastolic hypertension alone.

6. Among the 43 cases of congenital heart disease, ventricular septal defect made up almost half, namely, 21; auricular septal defect was diagnosed in 5 cases, subaortic stenosis in 4, coarctation of the aorta in 3, pulmonic stenosis in 3, patent ductus arteriosus in 2, and tetralogy of Fallot in 1. There were 4 other miscellaneous cases.

7. The most common cause for previous rejection in the group of 1A conservative cases was rheumatic heart disease, 79 cases out of 188 (42 per cent); arterial hypertension was second with 52 cases (28 per cent), and neurocirculatory asthenia was third with 17 cases (9 per cent); unspecified heart disease had been diagnosed in 27 cases and congenital heart disease in 5.

Disabling mitral regurgitation on the basis of an apical systolic murmur had been diagnosed wrongly, we thought, in 43 cases. Mitral stenosis had been diagnosed wrongly in 11, aortic stenosis in 4, aortic regurgitation in 3, and both mitral and aortic valve disease in 1. Disabling tachycardia had been diagnosed in 2. Heart block had been reported in one case in which there was obviously simply an intermittent pulse due to the frequent occurrence of premature beats.

8. In the borderline group which we at first labeled "1A liberal," the chief cause for rejection had been arterial hypertension, in 46 cases out of the 114 (40 per cent). The next most common cause for rejection was rheumatic heart disease, in 30 cases (26 per cent). Neurocirculatory asthenia had been diagnosed in 15 (13 per cent), unspecified heart disease in 12, and disabling tachycardia in 6.

9. The most difficult problems were three in number.

A. The determination of the normal blood pressure range.

B. The interpretation of slight systolic murmurs at the apex.

C. The diagnosis of neurocirculatory asthenia.

It was frequently necessary for all of the group to confer about some of these cases and even then the opinions were occasionally divided. It was for that reason that the borderline group was listed for further study. This included (a) cases with blood pressures a little above the limits ordinarily regarded as the upper range of normal, that is, between 150 and 170 systolic, or between 90 and 95 diastolic; (b) cases with systolic murmurs louder than grade 1 but not louder than grade 2 at the apex; (c) cases with heart rates above 100 and up to and including 120 after resting; and (d) cases with heart size by x-ray above the standards set for the normal upper limit (a transverse diameter up to 1 cm. beyond that calculated), namely, with transverse diameter up to 2 cm. above the expected measurement, provided nothing else was wrong and provided the build of the individual (wide chest and short stature) was in keeping.

10. Two interesting by-products of these re-examinations were: our observation of the attitudes of the men themselves, and a notation of their suitability for the particular work they were doing. In the great majority of cases, the morale of the men seemed to be excellent although a good many were obviously disappointed at not being in uniform. They had become, for the most part, reasonably well adjusted to their rejected status.

The work being carried on by the rejectees was extraordinarily varied and in the main very useful, much of it having to do directly with the war effort, as, for example, employment in shipyards. Only a very few of the men were unable to work at all because of their heart condition.

Attention to their medical needs seemed to have been satisfactory, but we gave further advice here and there as needed, particularly telling them to keep in touch with their own doctors if there was any particular reason for close follow-up.

CONCLUSIONS AND SUGGESTIONS

1. It has been evident from this re-examination in Boston that the care with which individuals having or suspected of having, heart disease or neurocirculatory asthenia have been analyzed and rejected by the local boards and Boston Induction Station has, without doubt, kept low the actual admission of cardiacs into the Army, but, quite possibly, it has excluded a certain percentage of normal men. It is to be expected that such a re-examination as has been carried out by the Special Medical Advisory Board would raise the problem of the range of the normal heart, and result in the recommendation for acceptance of a certain number of those who, at the time of the first examination, were considered doubtful or abnormal.

2. It is possible that a slightly more liberal interpretation of the heart rate, blood pressure, and heart murmurs may reduce the number of cases rejectable, on findings which may be within the range of normal as noted in the present report.

3. Further consideration should be given as to whether all, some, few, or none of the additional criteria for more liberal interpretation of the findings as expressed in this report, called borderline or "1A liberal," may reasonably be added to MR 1-9 for admission to the Armed Services. We have been especially impressed by the unimportance of sinus tachycardia per se, also by the frequency of slight and transient, probably unimportant, elevation of blood pressure (in particular systolic), and by the normal occurrence of very slight heart murmurs in excited young men with active circulations. This group, which we have labeled "borderline" or "1A liberal," is an important one for us to follow in the future from the standpoint of adding to our knowledge of the range of the normal heart. We cannot yet speak with certainty about some of these points, especially the blood pressure and murmurs; perhaps we never shall be able to do so, but such may be possible after further experience in the majority of cases. Appended to this report are some letters from various examiners of our special board, expressing individual opinions concerning some of the moot points.

4. The diagnosis of neurocirculatory asthenia must be based primarily on the history of symptoms and on neuropsychiatric analysis. In these civilians the condition is evident or latent, chiefly in neuropsychiatric cases, in contrast to the less important, although temporarily incapacitating, neurocirculatory asthenia that may involve the more rugged soldiers as the result of all kinds of strain from battle, infection, or other cause for fatigue. Therefore, we consider neuropsychiatric analysis of candidates for military service of prime importance for the detection and elimination of individuals who would be prone to neurocirculatory asthenia.

5. It is evident to us in Boston that this study has been of value, not so much for the salvage of men for the Armed Services, as, particularly, for the clarification of the problems that face the medical examiner of the new recruit and for pointing the direction for future research.

We wish to take this opportunity to express to the Selective Service, to the Medical Department of the Army, and to the civilian workers who have carried out this study, our great appreciation and thanks.

PAUL D. WHITE
Chairman of Boston Special Advisory Board

LETTERS FROM EXAMINERS

Dear Paul:

Thrills.—The notation of thrills should be abandoned entirely. When a thrill is marked and readily timed, there is always a murmur. The thrill is then of no aid in diagnosis. When it is faint it often leads the examiner astray.

Systolic Murmurs.—The most important single notation is the intensity of a murmur. All systolic murmurs of grade 3 intensity or louder should disqualify the selectee. All grade 1 murmurs should be disregarded unless there is other evidence of heart disease or unless there is a definite history of rheumatic infection. If there is only a grade 1 systolic murmur and the rheumatic infection took place more than five years before, if everything else is normal and the man appears fit, he may be

acceptable as "1A liberal." Grade 1 or grade 2 pulmonary systolic murmurs can be accepted as 1A conservative. Apical grade 2 systolic murmurs with heart rate 80 or under, are not acceptable. Grade 2 systolic murmurs with heart rates over 100, with no other evidence of heart disease, can be classified as "1A liberal." Heart rates between 80 and 100 with grade 2 systolic murmurs are open to question.

Heart Rate.—A normal sinus rate of 120 or less should be regarded as insignificant. A resting heart rate of over 120 should disqualify the selectee.

Blood Pressure.—Readings of 160 systolic and 95 diastolic or less, on the first examination or after one-half hour rest period, should be acceptable.

S. A. LEVINE

Dear Dr. White:

Although I took no active part in the discussion at our meeting last Tuesday, I did have some thoughts on the matters discussed. I am in entire agreement that simple tachycardia per se should not be a bar to acceptance into the Armed Forces. In the matter of murmurs, I am in agreement with the last memorandum which you sent out, except that I have wondered about the advisability of accepting grade 1 apical systolic murmurs in the absence of a history of rheumatic fever, and rejecting those with a murmur of the same intensity but with a history of rheumatic fever. In view of the frequency with which diastolic murmurs are found in the absence of positive rheumatic history, it would seem wiser to me to classify on the basis of physical signs alone, and that all grade 1 apical systolic murmurs be accepted or all rejected, but I favor the former.

In the matter of the blood pressure, about which there seemed to be considerable difference of opinion, it seems to me that the crux of the situation lies in General Hillman's report. Presumably, the total number of recruits with borderline or slightly elevated blood pressure is small, and if the numbers of such soldiers who have gotten into difficulties have been great enough to come to General Hillman's attention, it would seem that the problem would be an important one if the number of such recruits were to be increased. Furthermore, I have wondered how great the yield in man power would be if the standards were lowered within reasonable limits. Our experience with the 1,009 rejectees would indicate that the Army would gain only a handful of men out of the thousands examined in Metropolitan Boston.

Sincerely,

NORMAN H. BOYER

Dear Paul:

Here are my thoughts in regard to hypertension and tachycardia as involved in Army induction examinations.

Hypertension.—In regard to elevated blood pressure there are two basic questions to be considered: (1) is the Army interested in men who will make effective soldiers now and in the immediate future, i.e., for perhaps five years, only; or is it also trying to weed out men who will ultimately develop arterial hypertension and its complications, i.e., in ten to forty years; (2) are blood pressure measurements to be employed to discover instances of primary or secondary hypertension only, or else as an objective measure of other types of conditions, especially neurocirculatory asthenia?

I do not believe that men who, we think, will make good soldiers at the present time, but who may ultimately develop hypertension should be excluded from the Army, on the ground that they may ultimately become a charge on the Government, because: (a) we know altogether too little about the detection of hypertension in its incipient or prehypertensive stage; (b) we can tell even less about the rapidity with which hypertension will progress and develop complications in the individual case (with the exception of severe benign or malignant types); (c) we do not know what the policy of the country will be in regard to pensions, etc., after this war, and

the social security program may well bring many of these people under government care even if they have not served in the Army.

Therefore, our problem is to select and weed out men who may get into trouble in the next few years. In regard to this there are no data as to how much, if at all, the rigorous physical conditions of Army life and the state of fear and anxiety in combat situations aggravate early hypertension and precipitate vascular disasters. We must assume they do to some extent. I believe we should exclude men who we really think have significant hypertension at the present time, and my blood pressure criteria for such exclusion would be: a persistent pressure above 160 systolic and 90 diastolic after 30 minutes rest, with the exceptions that, in men with unusually thick (especially muscular) arms, an extra 5 mm. in both systolic and diastolic pressures may be allowed; and also, in the absence of all other reasons for rejection, systolic pressures up to 170 may be allowed provided the diastolic is 80 or below.

In regard to the second question: although abnormal blood pressure measurements may be corroborative of conditions other than primary or secondary hypertension, such as neurocirculatory asthenia, hyperthyroidism, aortic regurgitation, etc., by themselves they are insufficient evidence of any of these, and therefore by themselves should never be the occasion for such diagnoses.

Tachycardia.—In the presence of tachycardia of over 100, conditions such as recent acute infections, neurocirculatory asthenia, hyperthyroidism, heart disease, etc., should be particularly sought for by symptoms and signs, and if the heart rate is over 120 after 30 minutes rest, an electrocardigram should be taken. Simple tachycardia, without any other evidence of disqualifying disease, should not be a cause for rejection unless, after 30 minutes rest, it is over 140.

I enjoyed taking part in the examinations very much and learned a good deal from them, mainly because of the opportunity to compare opinions with you and the others. It seems to me that they were very worth while, not so much from the point of view of the rejectees that we re-examined, as from the knowledge and experience which was gained by all of us, which should be of help in establishing standards for the future. I certainly hope that the men we examined will be followed up in the future.

With best regards,

Sincerely,

LARRY ELLIS

Dear Dr. White:

The observations on neurocirculatory asthenia in this study demonstrated that there is far from unanimity in the definition and diagnosis of this condition.

In 35 cases in which the diagnosis had been made, our group did not substantiate this diagnosis, and the men were put in 1A. In 28 cases the diagnosis of neurocirculatory asthenia was substantiated, and the men were kept in 4F. In 14 cases the diagnosis was changed from neurocirculatory asthenia to some other cardiovascular diagnosis, usually hypertension, and the patient was retained in 4F. In 37 cases the patient who had been turned down for some other reason was kept in 4F with the diagnosis of neurocirculatory asthenia. In other words, we were in agreement with the original diagnosis in 28 cases, and we were in disagreement in 86 cases; that is, we were in agreement with the original examiners in 25 per cent of the cases and in disagreement in 75 per cent of the cases.

The basis of disagreement was apparently, in large part, a matter of definition. It was the feeling of our group that the man's medical history, social history, and work history were more important in the diagnosis than signs such as pulse, blood pressure, and sweating. If the patients had suffered in the past from palpitations, breathing difficulties, chest discomfort, nervousness, or faint and dizzy spells, and these had interfered with the patient's work or activity, it was felt that the diagnosis of neurocirculatory asthenia was justified, and that the patient was not good

soldier material for unlimited service. Tachycardia or hypertension in the absence of previous symptoms we did not feel constituted a useful basis for the diagnosis of neurocirculatory asthenia.

It is desirable that a uniform method of diagnosis for this condition be established at induction boards and in service hospitals.

A related problem which I wish to comment on is that of hypertension. It has seemed to me highly impractical to try to decide in a given case whether a man has "nervous hypertension" or "real hypertension." I don't see that there is much practical importance, for military purposes, of deciding this point. In the absence of complicating heart disease or renal disease, I don't think there is any evidence to show that hypertension of any degree is a handicap in military service. It is true that from the insurance company's point of view a man with hypertension is a poor risk. However, from the Army's standpoint, there probably isn't any valid evidence to show that men with hypertension make poorer soldiers than men with normal blood pressure. Of course, the compensation element has to be considered, but since compensation problems are to such a great extent decided by nonmedical criteria, it does not seem useful to consider this problem in making medical recommendations.

Yours sincerely,

MANDEL E. COHEN, M.D.

ADDENDUM

Of the cases that were considered to belong to the 1A status by the Boston Advisory Board, the following disposition had been made up to Jan. 18, 1944. (The 188 returned by us as 1A were the basis for this group of 190 cases. Two borderline cases were inducted by mistake.)

Commissioned in Army	1	
Inducted, Army	73	
Inducted for limited service	1	
Inducted, Navy	22	
Inducted, Marine Corps	3	
Total		100
Reclassified 4F by Local Board:		
Peptic ulcer	1	
New fracture	1	
Epilepsy	1	
Underweight	1	
Total		4
Reclassified by Local Board:		
1-A-H	5	
2-A	2	
2-B	17	
3-A	6	
3-D	1	
Total		31
Rejected at Induction Station:		
Organic heart disease	2	
Congenital heart disease	1	
Arterial hypertension	3	
History of rheumatic fever	3	
Neuropsychiatric reasons	30	
Neurologic lesions	2	
Other medical reasons	14	
Total		55
Grand Total		190

REPORT OF THE CHICAGO BOARD

G. K. FENN, M.D., CHAIRMAN

OBJECT OF STUDY

THIS study was begun at the instance of National Selective Service and the National Research Council to determine the possible salvage of man power by a careful re-examination of men who had been rejected for military service because of cardiovascular disease.

PLAN

The Chicago Board was organized under the Advisory Chairmanship of Dr. James B. Herrick. The examiners were selected from those men who were competent to recognize the various forms of cardiovascular disease. The Social Service Department of St. Luke's Hospital, Chicago, was selected as the site of the examinations. The Board elected to meet three times weekly, Tuesday and Thursday evenings and Saturday afternoon. The members of the Board were arranged in three groups in order to meet this arrangement, which, however, was soon abandoned, the Saturday afternoon period being given up. Thus, the Board was rearranged to meet the two evening periods each week. Lieut. Col. E. Mann Hartlett, Medical Director of Selective Service for Illinois, met with the Board at the organization meeting and assisted in the formulation of plans. Colonel Hartlett was at all times most helpful and cooperative and promptly met every request of the Board, although these were many and often burdensome.

PERSONNEL

Special Advisory Board No. 39

Advisory Chairman, Dr. James B. Herrick

Dr. G. K. Fenn, Chairman

Dr. Joseph A. Capps
Dr. George H. Coleman
Dr. R. A. Dolkart
Dr. Max P. Gethner
Dr. W. S. Gibson
Dr. N. C. Gilbert
Dr. L. E. Hines
Dr. Frank B. Kelly
Dr. J. Roscoe Miller
Dr. Carl O. Rinder
Dr. Sidney Strauss
Dr. Howard Wakefield

Dr. E. L. Jenkinson, and his staff, of the X-ray Department of St. Luke's Hospital, supplied all x-ray work and the interpretation thereof.

Mrs. Olga Marland, of the Electrocardiograph-Metabolism Department of St. Luke's Hospital, was in charge of integrating the work of the Board with the office of Selective Service. It was her untiring effort and attention to detail that permitted schedules to be met.

Mr. Leo M. Lyons and Dr. A. P. Merrill, of the Administrative Department of St. Luke's Hospital, put all of the necessary facilities of the hospital at the disposal of the Board.

Lieut. Col. E. Mann Hartlett, Medical Director of Illinois Selective Service, was responsible for supplying the men for examination. He always did this cheerfully and at the appointed time.

Clerical Assistants

Lydia Hencky	Margaret Voelker
Merrill Sutherland	Margaret Weeden
Margaret Thompson	Clare Weiner
Bernace Vander Linden	Marion Wickland

Electrocardiograph Technician

Josephine Knoll

PROCEDURE

Men were sent in by Selective Service from 52 of the local boards situated in the city of Chicago. The smallest number from any single board was one, and the greatest number from any single board was forty-seven. The men were examined, for the most part, on Tuesday and Thursday evenings, beginning at 6:30. The men were selected at random by order number from all of the boards, which were widely scattered throughout the city. The only requirement was that they must have been rejected by the local board or induction center because of cardiovascular disease only. The usual number to report for examination at one session was 60 to 70. The smallest number to report at one time was 18 and the largest number was 109.

A special form, labeled Special Examination of Rejectees With Cardiovascular Defects (DSS Form 1003), was distributed to the local boards. These forms were partly filled out by the local board and were sent by mail, together with the local board or induction station record, to the examining station at St. Luke's Hospital. It was arranged that these records would arrive a few days in advance of the time that the men were required to report for examination.

In all, 1,082 men were registered at the examining station. Of this number, 15 were found to have been rejected for causes other than cardiovascular disease; 37 men were found to have disqualifying defects in addition to cardiovascular disease. This left 1,030 men who qualified for examination in this study. On the last evening of the study, 93 men reported for examination but none of these 93 was recommended for transfer from 4F to 1A. Consequently, the last thirty records were set aside to bring the number to 1,000 men. This made no difference in the number of men transferred from 4F to 1A and made but a small fraction of 1 per cent of difference in the calculation of the causes for rejection.

At every session of the Board, the proportionate number of records were distributed among the members. Many of the records contained reduced x-rays and electrocardiograms. Whenever there was doubt concerning any examinee, a conference of examiners was held. X-rays and electrocardiograms were made routinely on all men recommended for transfer from 4F to 1A.

As a general thing, the instructions contained in War Department MR 1-9 were closely adhered to. In all doubtful cases, 2 meter chest films were made so that the Hodges-Eyster formula might be applied, and electrocardiograms were made. In every case the x-ray and the electrocardiogram were reviewed by the examining physician and by the chairman of the Board.

1. Rheumatic heart disease offered no great difficulty except as far as accuracy in diagnosis of the lesion was concerned. A certain number of cases were obviously unfit for military service, but insufficient time was spent with them to be reasonably certain of the accurate diagnosis. These are listed as unclassified.

2. The hypertensives offered the greatest problem. The Board adhered to the instructions in MR 1-9, but it feels that it is here, if any place, that more liberality might have been shown.

3. The Hodges-Eyster formula was applied to govern excessive heart size. The Board feels that this is not the ideal method of judging increase in heart size. Nine men were rejected because of increase in heart size alone. Two men who were found to have increased heart size were recommended for transfer from 4F to 1A.

4. The Board doubts that the true incidence of syphilitic heart disease is represented by 0.5 per cent.

RECOMMENDED FOR TRANSFER FROM 4F TO 1A

Thirty-eight of these examinees were recommended for transfer from 4F to 1A. While the rejections as a rule did not offer much of a problem, the men who were transferred required very careful study indeed. Only twelve of the thirty-eight were found by the examiners to have no abnormal cardiovascular findings.

In the case of the remaining twenty-six, careful study was required to decide whether or not the abnormal findings were significant. Apart from the electrocardiographic phenomena, which will be discussed under the laboratory work, Table I presents the incidence of abnormal physical findings.

CHICAGO. TABLE I

Systolic murmur (not significant)	9
Systolic murmur (not significant) plus slight increase in heart size	1
Transient tachycardia	2
Transient tachycardia plus slight increase in heart size	1
Transient hypertension	2
	15

The remaining eleven had electrocardiographic findings only.

The Board, after considering all of the evidence, sent this group of thirty-eight men back to the induction center for Class 1A. Colonel Hartlett has promised the Board that he will obtain the Army serial numbers of these inductees. It is proposed to pool these numbers with others obtained in a similar fashion so that the progress of these men may be observed. The local board and induction station diagnoses in these thirty-eight men are given with the individual records.

CHICAGO. TABLE II

EXAMINER	NUMBER EXAMINED	4F TO 1A	%	REJECTION DIAGNOSIS (LOCAL BOARD OR INDUCTION STATION)
Capps	50	None	0	
Coleman	124	5	4	(1) Intermittence of heart beat; (2) hypertrophy and tachycardia; (3) valvular heart disease with mitral regurgitation; (4) heart murmur; (5) tachycardia
Dolkart	12	None	0	
Gethner	120	None	0	
Gibson	37	3	8.1	(1) Mitral regurgitation; (2) heart disease; (3) hypertension
Gilbert	42	2	4.7	(1) Heart murmur; (2) valvular heart disease
Hines	88	7	8	(1) Rheumatic heart disease; (2) hypertension and tachycardia; (3) tachycardia; (4) hypertensive heart disease; (5) cardiac disease; (6) hypertension; (7) enlarged heart
Kelly	83	None	0	
Miller	115	10	9	(1) Hypertension; (2) chronic myocarditis; (3) tachycardia; (4) chronic valvular heart disease; (5) tachycardia; (6) mitral stenosis; (7) mitral lesion; (8) chronic valvular heart disease; (9) valvular heart disease; (10) valvular heart disease with mitral insufficiency
Rinder	91	3	3.3	(1) Systolic murmur; (2) heart murmur; (3) heart murmur
Strauss	59	5	6.9	(1) Systolic murmur and tachycardia; (2) tachycardia and valve disease; (3) systolic murmur on exercise; (4) chronic valvular heart disease with mitral insufficiency; (5) chronic valvular heart disease
Wakefield	164	2	1.3	(1) Chronic valvular heart disease; (2) myocardial damage
Fenn	10	1	10	Chronic valvular heart disease

INDIVIDUAL RECORDS

Table II gives the number of men recommended for transfer from 4F to 1A by each examiner. Included in this list is the number of men examined by each examiner and the percentage recommended for transfer by each examiner. The rejection diagnosis by the local board or induction station is also given.

LABORATORY WORK

In all, sixty-eight electrocardiograms and x-rays, three basal metabolic rates, two urinalyses, and one erythrocyte sedimentation rate were

carried out at the direction of the Board. Many other electrocardiograms and x-rays that had been made elsewhere were reviewed by the Board.

The basal metabolic rate determinations were +30 per cent, +23.5 per cent and –11 per cent. All of these men were rejected. One urinalysis was negative. The other showed the presence of albumin and casts. Both of these men were rejected. The erythrocyte sedimentation rate was within normal limits. This man was transferred from 4F to 1A.

Electrocardiograms and 2 meter chest films were studied in the case of all men transferred from 4F to 1A. The Hodges-Eyster formula was applied to all chest films. With two exceptions, the heart size and contour were normal in all of these x-rays. In two cases, previously mentioned, the actual heart size slightly exceeded the calculated size.

In eighteen of the thirty-eight men recommended for transfer from 4F to 1A, the electrocardiograms were quite normal. In the remaining twenty men the electrocardiogram showed some abnormality. The most common aberration was that of right axis deviation. The Board realizes that axis deviation does not indicate cardiac pathology, but it was rather surprising to find such a large number of right axis deviation curves in this group. It occurred three times alone, and seven additional times with some other finding. Thus, it occurred ten times: in one-half of the cases showing electrocardiographic aberrations, and in 27 per cent of the total number transferred from 4F to 1A. In eleven instances the electrocardiographic change was the sole aberration; in nine instances such changes were associated with other findings.

Electrocardiographic Change Alone		
Right axis deviation alone	3	
Right axis deviation plus aberrant QRS	1	
Right axis deviation plus depressed S-T segment	1	
Left axis deviation	2	
Depression or elevation of S-T segments alone	2	
Depressed T waves alone	2	11
Electrocardiographic Change Plus Other Finding		
Right axis deviation plus systolic murmur	2	
Right axis deviation plus transient hypertension	2	
Right axis deviation plus transient tachycardia	1	
Prolonged P-R interval plus systolic murmur	1	
Aberrant QRS plus systolic murmur	1	
Depressed T waves plus systolic murmur	1	
Marked sinus arrhythmia with nodal escape plus systolic murmur	1	9
Total	20	

In the group that was rejected or continued in Class 4F, thirty x-rays and electrocardiograms were made at the request of the Board. In fourteen instances the x-rays were quite normal. In twelve of these cases the electrocardiograms were also normal, but the men were re-

jected because of persistent tachycardia, hypertension, neurocirculatory asthenia, or some other cause. In two of these cases the electrocardiograms were somewhat abnormal, one showing frequent premature ventricular systoles together with a marked sinus arrhythmia and the other a depressed T wave in Lead IVF together with a left axis deviation and a deeply inverted T_3.

In twelve instances the heart size was more than 1 cm. greater than the predicted size. In nine of these cases no other reason was found for rejection. In three cases the electrocardiograms were also abnormal.

In three instances the heart was within normal limits but had a distinct mitral configuration. In all three of these the electrocardiograms were questionable.

In one instance the x-ray seemed to establish a diagnosis of active pulmonary tuberculosis.

Tables III to XVI represent a tabulation of the causes for rejection in 962 cases that were continued in Class 4F.

CHICAGO. TABLE III

PERCENTAGE OF REJECTIONS IN EACH CATEGORY

CATEGORY	TOTAL CASES (%)	REJECTED CASES (%)
Rheumatic disease	64.8	67.25
Hypertension	19.6	20.0
Congenital heart disease	2.8	2.9
Tachycardia	2.4	2.4
Hyperthyroidism	0.8	0.8
Arrhythmia	0.5	0.5
Unclassified	2.8	2.9
Hypertrophy	0.9	0.9
Syphilis	0.5	0.5
Neurocirculatory asthenia	1.1	1.1

CHICAGO. TABLE IV

RHEUMATIC HEART DISEASE

	NO.	PER CENT
Total examinations	1,000	
Rejected for rheumatic heart disease	648	64.8
Total rejections	962	
Percentage of rejectees with rheumatic disease		67.25
Mitral disease	292	45.0
Mitral insufficiency only	144	22.2
Aortic disease	10	1.5
Aortic insufficiency only	37	5.8
Mitral and aortic	125	19.2
Unspecified*	37	5.8
Rheumatic fever†	3	0.5

Eleven of these men were found to have auricular fibrillation in addition to the other signs of rheumatic heart disease.

*Diagnosis of rheumatic heart disease only, lesion unspecified.

†Rejected because of active rheumatic fever or recent rheumatic fever. No demonstrable heart lesion present.

CHICAGO. TABLE V

CAUSE FOR REJECTION BY LOCAL BOARD OR INDUCTION CENTER* OF 648 SELECTEES REJECTED UNDER GENERAL DIAGNOSIS OF RHEUMATIC HEART DISEASE

Chronic valvular heart disease, unspecified	171
Chronic valvular heart disease, with mitral insufficiency	95
Chronic valvular heart disease, with mitral stenosis	77
Chronic valvular heart disease, with aortic insufficiency	38
Chronic valvular heart disease, with mitral and aortic disease	30
Rheumatic valvular disease	38
Organic heart disease	20
Cardiac hypertrophy	19
Mitral insufficiency	15
Chronic valvular disease, with double mitral	15
Mitral murmur	15
Heart trouble	14
Large heart with mitral murmur	12
Hypertrophy with mitral regurgitation	12
Tachycardia	18
Mitral stenosis	8
Systolic murmur	7
Heart lesion	5
Cardiovascular disease	5
Auricular fibrillation	5
Mitral lesion	4
Aortic diastolic murmur	3
Pericarditis	3
Congenital heart disease	3
Leakage of the heart	2
Systolic and diastolic murmur	2
Myocardial damage	2
Chronic valvular disease, with aortic stenosis	2
Mitral heart disease	2
Arterial hypertension with myocardial damage; mitral and double aortic murmurs; tachycardia with valvular incompetence; thyrotoxicosis and myocarditis; cardiac pathology; aortic obstruction; murmur over valvular heart; rheumatic fever; chronic valvular disease with double aortic; cardiac arrhythmia; heart block; bilateral ocular nystagmus (one each)	12
	648

Of this group, four were Filipino, thirty-nine were Negro, and 605 were white.
*DSS Form 1003.

CHICAGO. TABLE VI

HYPERTENSION

(The Board rejected for hypertension or hypertensive heart disease a total of 196 selectees. In all cases the systolic pressure was more than 150 mm. with the exception of three cases in which the systolic was within normal limits but the diastolic pressure was more than 100 mm.)

DIASTOLIC PRESSURE	REJECTIONS
90-110	57
110-130	57
130-150	15
150 plus	3
Systolic only elevated	27
Diastolic only elevated	3
Unspecified	34
	196

CHICAGO. TABLE VII

CAUSE FOR REJECTION BY LOCAL BOARD OR INDUCTION CENTER* OF 196 SELECTEES IN TABLE VI

Hypertension or hypertensive heart disease	121
Tachycardia	17
Chronic valvular heart disease, unspecified	9
Chronic valvular heart disease, mitral insufficiency	8
Hypertrophy	6
Cardiac lesion	6
Heart disease	4
Systolic murmur	4
Rheumatic heart disease	3
Organic valvular disease	2
Hyperthyroidism	2
Mitral heart disease	2
Double mitral lesion; bronchial asthma (cardiac); cardiovascular disease; nephritis; heart condition; intraventricular block; heart shadow; chronic endocarditis; hyperactive unstable; psychomotor tension; aortic heart murmur; mitral stenosis (one each)	12
	196

Of this group, 23 were Negro; the remainder were white.
*DSS Form 1003.

CHICAGO. TABLE VIII

CONGENITAL HEART DISEASE

(The Board rejected 28 selectees under the diagnosis of congenital heart disease)

Patent ductus arteriosus	6
Patent interventricular septum	9
Coarctation of aorta	2
Unspecified	11
	28

One of the cases of patent ductus had also a dextrocardia.

CHICAGO. TABLE IX

DIAGNOSIS GIVEN BY LOCAL BOARD OR INDUCTION CENTER IN CASES IN TABLE VIII

Congenital heart disease	5
Congenital heart disease, patent ductus arteriosus	6
Chronic valvular disease	4
Coarctation of aorta	2
Chronic valvular disease, mitral insufficiency	2
Heart disease	1
Hypertrophy	1
Mitral systolic and pulmonary heart murmur	1
Rheumatic cardiovascular disease, mitral and aortic	1
Systolic mitral murmur	1
Aortic and mitral murmur	1
Valvular heart disease	1
Cardiac lesion	1
Tachycardia	1
	28

Congenital heart disease was found only in the white selectees.

CHICAGO. TABLE X

TACHYCARDIA

(The Board rejected 24 men because of tachycardia. The diagnosis given in these cases by the local board or induction center is shown)

Tachycardia	17
Hypertrophy	2
Nervous twitching	1
Chronic valvular disease, mitral insufficiency	1
Mitral systolic murmur	1
Heart trouble	1
No cause assigned	1
	24

There were white men only in this group.

CHICAGO. TABLE XI

HYPERTHYROIDISM

(The Board rejected eight men because of hyperthyroidism. The diagnosis given by the local board or the induction center is shown)

Hyperthyroidism	4
Tachycardia	3
Valvular heart disease	1
	8

There was one Negro in this group.

CHICAGO. TABLE XII

ARRHYTHMIA

Five men were rejected because of electrocardiographic abnormalities only. These were classified as follows:

Myocardial damage (electrocardiogram)	2
Pulsus bigeminus	1
Sinoauricular block with frequent premature ventricular systoles	1
Bundle branch block with pulsus alternans	1
	5

The local board or induction center diagnosis in these cases was as follows:

Myocardial damage	2
Cardiac disease; nodal rhythm; bundle branch block (one each)	3
	5

There were five additional cases in which serious arrhythmias were found. These cases are listed here but should not be included in the totals as they have been included in the rejections elsewhere

LOCAL BOARD OR INDUCTION CENTER	REJECTED BY SPECIAL BOARD FOR
1. First degree A-V block	1. A-V block. Rheumatic heart disease with mitral insufficiency
2. First degree A-V block	2. Rheumatic heart disease with mitral insufficiency
3. Valvular heart disease	3. Rheumatic mitral disease with bundle branch block
4. Intraventricular block	4. Hypertensive heart disease
5. Bundle branch block	5. Bundle branch block with rheumatic mitral disease

CHICAGO. TABLE XIII

UNCLASSIFIED

(There were 28 instances in which the examiner made no specific diagnosis. These were cases in which the presence of disqualifying heart disease was obvious but in which the record does not permit accurate classification. The diagnosis given by the local board or induction station is shown)

Chronic valvular disease	14
Hypertrophy	3
Organic heart disease	3
Heart disease	2
Dilatation of heart; syphilis; cardiac damage; congenital heart disease; aortic heart disease; systolic murmur (one each)	6
	28

One Negro is included in this group.

CHICAGO. TABLE XIV

HYPERTROPHY

(Nine men were rejected for hypertrophy only. Enlargement was calculated on the basis of the Eyster-Hodges formula as directed. Diagnosis is shown)

Hypertrophy	3
Rheumatic heart disease	2
Aortic systolic murmur; heart finding; valvular heart disease with mitral insufficiency; no cause (one each)	4
	9

CHICAGO. TABLE XV

SYPHILIS

(In five instances the Board made a diagnosis of syphilitic heart disease. The diagnosis of the local board or induction station is shown)

Hypertension	2
Aortitis	1
Chronic valvular disease	1
Angina pectoris	1
	5

There were no Negroes in this group.

CHICAGO. TABLE XVI

NEUROCIRCULATORY ASTHENIA

(In eleven instances the Board made a diagnosis of neurocirculatory asthenia. The admitting diagnosis in these cases is shown)

Tachycardia	4
Valvular heart disease	2
Hypertension and tachycardia	1
Hypertrophy	1
Aortic insufficiency	1
Heart murmur	1
Cardiac disease	1
	11

SUMMARY

Number of men examined and credited to study				1,000
Transferred from 4F to 1A			38	
Rejected, white	892	(Only white selectees transferred from 4F to 1A)		
Negro	66			
Filipino	4			
	962		962	
				1,000

Rheumatic disease		648
white	605	
Negro	39	
Filipino	4	
Hypertension		196
white	173	
Negro	23	
Congenital		28
white only		
Tachycardia		24
white only		
Unclassified		28
white	27	
Negro	1	
Arrhythmias		5
white only		
Hyperthyroid		8
white	7	
Negro	1	
Hypertrophy		9
white	7	
Negro	2	
Syphilis		5
white only		
Neurocirculatory asthenia		11
white only		
		962

ADDENDUM

As of Jan. 1, 1944, the status of the thirty-eight men transferred from 4F to 1A was as follows:

Accepted by Army	17
Accepted by Navy	2
1A classification	2
2A classification	2
2B classification	3
4H classification	2
Rejected because of heart defect	3
Rejected because of defect other than heart	7
Total	38

REPORT OF THE NEW YORK BOARD

ROBERT L. LEVY, M.D., CHAIRMAN

PLAN OF STUDY

THE registrants were chosen by the office of the Medical Division of Selective Service Headquarters in New York City. Names were selected from the files of each of the 123 local boards scattered through the boroughs of Manhattan and the Bronx. Men from other boroughs were not included, because of the longer time required for transportation and because it was believed that the material represented a fair sample. An attempt was made to select cases in which the sole cause for rejection was cardiovascular disease; only in a few instances were other defects present. In all, 1,014 men were examined. Several cases were discarded because the cause for rejection was not primarily cardiovascular; one man, for example, had pulmonary tuberculosis and had been treated surgically by thoracoplasty. In a few other instances, associated conditions complicated the situation. The 1,000 cases finally chosen for study met the necessary requirements in a satisfactory manner.

Each local board notified the rejectee to report to the Vanderbilt Clinic of the Presbyterian Hospital at a specified time. The records of the local board and those of the Induction Station, when the registrant had been examined there, were sent to the Chairman of the Examining Board in advance. Electrocardiograms and x-rays, when available, accompanied these records.

Sessions were held on Tuesday and Thursday evenings, beginning at 6:30, and on Saturday afternoons, beginning at 1:30. There were fourteen such sessions, from February 9 to March 11, 1943. From 50 to 110 men were examined at various sessions; during the final period only 14 men were examined to serve as replacements for discarded cases.

A special printed record form, provided by Selective Service Headquarters in Washington, was employed. The first portion was filled out by the clerk at the local board and gave the essential facts concerning the registrant, together with the place and cause of rejection. Below this, the examining physician filled out the history and results of the examination. In making the final analysis of the data, a special coded statistical form was employed from which the tables given in this report were compiled. In the course of the work it was not found necessary to make examinations of the blood or urine, and the exercise test was not considered of sufficient value to be used. The classification employed for final diagnosis was one which had been agreed upon for use in all

of the five cities making these examinations and was based upon the nomenclature recommended by the American Heart Association, though somewhat simplified. To each examiner was given a typewritten list of directions for filling out the charts, together with the nomenclature.

It was arranged with Selective Service that the registrants regarded as not having cardiovascular disease, and therefore reclassified from 4F to 1A, were to be resubmitted to the Induction Station in New York City. A recommendation was made by Brig. Gen. C. C. Hillman, of the Surgeon General's Office, to Col. C. M. Walson, Chief of the Medical Branch, Second Service Command, that the men resubmitted be accepted for active military duty. Colonel Walson has agreed to send to the Chairman of the Special Medical Advisory Board the Army serial number of each man accepted, in order that later he may be traced and his health record and performance in the service may be scrutinized. This group of cases, if so followed, should furnish a valuable check on the validity of the revisions in diagnosis.

PARTICIPANTS IN THE STUDY AND ACKNOWLEDGMENTS

Thirteen physicians, four secretaries, six technicians and two aides constituted the personnel. All were generous with their time and services. The membership was as follows:

Senior Examiners.—Drs. Arthur C. DeGraff, Clarence E. de la Chapelle, B. S. Oppenheimer, Harold E. B. Pardee, Howard F. Shattuck, and Robert L. Levy (Chairman).

Assistant Examiners.—Drs. John M. Baldwin, Jr., Adolph R. Berger, Edwina Campbell, John L. Caughey, Jr., William M. Hitzig, Donald D. Parker, and Grant Sanger.

The senior and assistant examiners constituted Special Medical Advisory Board No. 30.

Secretaries.—Mrs. Edward Armatys, Mrs. John M. Baldwin, Jr., Miss Dorothy R. Bramwell, and Miss Margaret Lawlor.

Technicians.—Miss Helene V. Armstrong, Miss Addie Bauer, Miss Elizabeth Howard, Miss Mary Pembleton, Miss Dorothy Rose, and Mr. Maurice Tate.

Aides.—Mrs. Harry Aranow, Jr., and Miss Barbara Levy.

The facilities of the X-ray Department of the Presbyterian Hospital were made available through the kindness of Dr. Ross Golden, the Director. Dr. Lois C. Collins interpreted and measured all of the chest films. The electrocardiograms were taken with two mobile Cambridge machines and were read by Dr. Robert L. Levy.

Miss Dorothy Kurtz, Supervisor of the Record Department of the Presbyterian Hospital, rendered invaluable help in making the statistical analyses.

Mr. John F. Bush, Executive Vice-President of the Presbyterian Hospital, placed at our disposal one wing on the second floor of the Vanderbilt Clinic; and the Director of the Clinic, Dr. Frederick MacCurdy, saw to it that every facility was at hand.

The project had the support of Col. Arthur V. McDermott, Director of Selective Service for New York City. Through the splendid cooperation of Col. Samuel J. Kopetzky, Chief of the Medical Division, the registrants were chosen, the notices were sent out to the local boards, and all necessary records were handled. Without his constant help the work could not have been carried through to a successful conclusion. A copy of his letter of instruction to the chairman of each local board is appended.

PROCEDURE

Each registrant was seen by at least two of the members of the board, one of whom was a senior examiner. Each case regarded as a candidate for resubmission had a four-lead electrocardiogram and a 2 meter x-ray film of the chest at the conclusion of the physical examination, so that a return visit was not necessary. Interesting cases or those in which the diagnosis was in doubt were seen, as a rule, by most of the examiners present. Unusual or borderline electrocardiograms were discussed by at least three of the senior examiners. Final decision on the cases having electrocardiographic and x-ray examinations was made in every instance by the Chairman of the Board, who had before him the clinical record and the laboratory findings. In making the final diagnosis, all of these were taken into account.

The height and weight were recorded only in those who had x-rays of the chest. This was done in order that the predicted transverse diameter of the heart could be calculated according to the Hodges-Eyster formula.

If the heart rate and blood pressure were normal, a second reading was not taken. If they exceeded the upper limits, both rate and blood pressure were taken again after thirty minutes' rest. Each registrant was examined in a small room, of which some twenty were available. He was allowed to lie quietly by himself, so that the second reading represented basal conditions as nearly as these could be obtained under the circumstances.

COMMENTS ON THE CRITERIA EMPLOYED

The criteria observed were, in general, those outlined in "Standards of Physical Examination During Mobilization," issued by the War Department on Oct. 15, 1942, and referred to as MR 1-9. The following notes present the interpretation placed upon some of these instructions by the New York Board:

1. *Rheumatic Fever or Chorea.*—If the rejectee had an authenticated attack of rheumatic fever or chorea within five years of the date of examination, he was not considered suitable for active service. By

"authenticated" is meant an illness of this sort substantiated by a letter from a hospital or a private physician; in certain cases, an adequate description of the illness by the registrant was considered sufficient. Rejection was made regardless of whether abnormal physical signs were found in the heart.

A registrant was rejected if there was a history of rheumatic fever or chorea, and if doubtful signs of disease were found in the heart. A persistent apical systolic murmur, even though not loud and not well transmitted, was regarded as abnormal under such conditions.

Registrants with a history of rheumatic fever or chorea which had occurred more than five years previously, with no abnormal physical signs, and with a normal electrocardiogram and teleroentgenogram, were resubmitted. A history of more than one attack did not influence this decision.

2. *Hypertension.*—A persistent systolic blood pressure of over 150, or a persistent diastolic of over 90, was considered a cause for rejection. If the systolic pressure was elevated to a level not over 170, the diastolic was normal and if, in the opinion of the examiner, such systolic hypertension was due to nervousness, an exception was made provided no other abnormal findings were present. The association of a normal heart rate with an elevation of systolic blood pressure was considered to be an unfavorable sign. A diastolic pressure above 90, even though the registrant was nervous, was cause for rejection.

A good many of those with hypertension had been sent for observation to the hospital at Fort Jay, on Governor's Island, where readings had been taken on several successive days. These records furnished helpful confirmatory evidence.

3. *Tachycardia.*—A heart rate of over 100 was considered abnormal. It was rare that persistent tachycardia was thought to be of nervous origin. When systolic hypertension also was present, the diagnosis not infrequently was neurocirculatory asthenia.

4. *Systolic Murmurs at the Apex.*—If the murmur persisted in both recumbent and erect positions, was of moderate intensity or loud, was transmitted to the axilla, and was not abolished or significantly diminished by forced breathing, it was considered to be evidence of organic mitral disease, regardless of other findings. Obviously, the presence of cardiac enlargement, an accentuated pulmonic second sound, or an abnormal electrocardiogram afforded added evidence of a cardiac disorder. In a few cases, moderate or loud systolic murmurs were heard which were clearly extracardiac, and in a few others a late systolic click was audible. Provided there were no other signs, the case was resubmitted. The to-and-fro scratchy sound sometimes heard along the left sternal border was considered to be cardiorespiratory in origin and was likewise disregarded.

5. *Systolic Murmurs at the Aortic Area.*—If not associated with any other abnormal finding, provided they were localized and not harsh, such murmurs were not regarded as a cause for rejection. The absence of a thrill did not influence the decision; the presence of a thrill strengthened the opinion that the murmur was significant. Diminution of the intensity of the aortic second sound emphasized the importance of such murmurs.

6. *Diastolic Murmurs.*—All were regarded as pathologic, regardless of location.

7. *Arrhythmias.*—The occurrence of extrasystoles was the only form of arrhythmia in which the decision occasionally was doubtful. If these occurred persistently coupled with normal beats and could not be diminished or abolished by exercise, the candidate was rejected. Such an example occurred but once. Occasional extrasystoles, either ventricular or auricular, were not regarded as a cause for rejection. In every instance the ventricular extrasystoles arose from a single focus, when recorded in the electrocardiogram. Cases with an authenticated history of paroxysmal tachycardia or paroxysmal auricular fibrillation were rejected. In several cases electrocardiograms taken during attacks were furnished by responsible observers or hospitals, so that the patient's statement could be confirmed. Permanent auricular fibrillation was seen only in association with organic cardiac disease. It was, of course, a cause for rejection.

8. *Coronary Occlusion.*—If there was a history of coronary occlusion with cardiac infarction, even though all signs, including the electrocardiogram, were normal, the registrant was rejected, provided he could produce electrocardiograms and clinical notes made at the time of his illness by a physician or in a hosptial. One case of this sort was seen.

9. *Electrocardiogram.*—Any significant deviation from the normal, regardless of whether all other findings were negative, was considered a cause for rejection. Significant findings were bundle branch block with QRS of more than 0.10 second; significant T wave negativity; low T waves in the limb leads (less than 1 mm.); significant RS-T deviation (more than 1 mm. above or below the isoelectric line in the limb leads and more than 2 mm. in Lead IVF); large Q waves in Leads I and IVF (more than 3 mm.); and incomplete heart block. A P-R interval over 0.20 second was considered abnormal. The occurrence of deep S waves in Leads I and II, axis deviation or notching of QRS, unaccompanied by widening of the QRS interval, was not regarded as a cause for rejection. In point of fact, these changes were found only in association with organic heart disease.

10. *X-ray* (2 meter film of heart).—If the transverse diameter of the heart exceeded the predicted transverse diameter, calculated according to the Hodges-Eyster formula, by more than 1 cm., the candidate was rejected even if all other findings were negative. Inasmuch as the Hodges-Eyster formula takes into account height and weight, and

hence variations in body build, as well as age, there was no exception made to this rule. Enlargement as an isolated finding was relatively uncommon; not infrequently it was found associated with some electrocardiographic abnormality, with an abnormal contour of the heart or with other physical signs indicative of disease.

Fluoroscopy was not employed.

11. *Neurocirculatory Asthenia.*—Except in advanced cases, the diagnosis of this condition was difficult on the basis of a single examination. The history was considered important. Tachycardia and moderate hypertension were usually, though not invariably, present. Cold, moist palms often furnished a helpful diagnostic sign. Psychiatric examination was not attempted.

12. *Extracardiac Causes for Rejection.*—Extreme funnel breast, with displacement of the heart to the left, deforming kyphoscoliosis, and severe rachitic deformities of the chest were causes for rejection. These often resulted in displacement of the heart and impaired its functional capacity. There was one instance of toxic nodular goiter with tachycardia, and one of aneurysm of the external carotid artery, traumatic in origin.

RESULTS

A detailed statistical analysis is given in the accompanying tables.

1. *Distribution and Recommendation by Age and Race* (Table I).—Of the 1,000 men examined, 805 were between the ages of 22 and 33 years. Only four were more than 37 years of age. One hundred and ninety-two (19.2 per cent) were considered not to have cardiovascular disease and were resubmitted. Of those resubmitted, the greatest number (78.2 per cent) were between 22 and 29 years of age. Of those rejected only 62.7 per cent were between these ages. The difference, though not great, is worthy of note.

NEW YORK. TABLE I

DISTRIBUTION AND RECOMMENDATION BY AGE AND RACE

AGE AND RACE GROUPS	TOTAL CASES EXAMINED	RESUBMITTED		NOT RESUBMITTED	
		NUMBER	PERCENTAGE	NUMBER	PERCENTAGE
TOTAL CASES	1000	192	100.0	808	100.0
18-21	77	13	6.8	64	7.9
22-25	358	90	46.9	268	33.2
26-29	298	60	31.3	238	29.5
30-33	169	15	7.8	154	19.1
34-37	94	13	6.7	81	10.0
38-41	3	1	0.5	2	0.2
42 and over	1			1	0.1
White	905	180	93.7	725	89.7
Negro	90	12	6.3	78	9.7
Chinese	5			5	0.6

	RESUBMITTED (%)	NOT RESUBMITTED (%)
Of total cases	19.2	80.8
Of total white	19.9	80.1
Of total Negro	13.3	86.7
Of total Chinese		100.0

The majority, namely 905 of the total number, were white; 90 were Negroes; and five were Chinese. Of the white men, 19.9 per cent were resubmitted, and of the Negroes, 13.3 per cent. All of the Chinese were rejected.

2. *Place and Cause of Original Rejection* (Table II).—Of the 1,000 cases, 494 had been rejected by the local draft boards and 506 by induction stations. As was anticipated, of those examined by the local draft boards a greater number (23.5 per cent) were resubmitted than was the case in those examined by the induction stations (15.1 per cent). At the induction stations there was a better opportunity for more careful examination, and in many cases, when the diagnosis was in doubt, the men had been sent to the hospital at Fort Jay for several days' observation.

NEW YORK. TABLE II

PLACE AND CAUSE OF REJECTION

PLACES AND DIAGNOSES	TOTAL CASES EXAMINED	RESUBMITTED		NOT RESUBMITTED	
		NUMBER	PERCENTAGE	NUMBER	PERCENTAGE
TOTAL CASES	1000	192	100.0	808	100.0
Local draft board	494	116	60.4	378	46.8
Induction station	506	76	39.6	430	53.2
REJECTION DIAGNOSES					
Heart disease, unspecified	87	20	10.4	67	8.3
Valvular heart disease, rheumatic	635	109	56.8	526	65.1
Congenital heart disease	18	1	0.5	17	2.1
Coronary heart disease	1			1	0.1
Hypertension	192	43	22.4	149	18.4
Tachycardia	96	27	14.1	69	8.5
Neurocirculatory asthenia	9	1	0.5	8	1.0
Cardiac hypertrophy	55	12	6.3	43	5.3
Cardiac arrhythmia	8	1	0.5	7	0.9
Aneurysm of aorta	1			1	0.1
Aneurysm other than aortic	1			1	0.1
Potential heart disease, rheumatic	1			1	0.1
Chest deformity	2			2	0.2

By far the commonest cause for rejection was rheumatic valvular heart disease, next in importance being hypertension. There followed, in the order of frequency, tachycardia, heart disease of unspecified etiology, cardiac hypertrophy, and congenital heart disease. The percentages among those resubmitted and those not resubmitted followed the same order.

3. *History and Clinical Examination* (Table III).—Of the total number of 1,000 cases examined, 679 had no symptoms, and 321 gave a story of either dyspnea on exertion, paroxysmal dyspnea, pulmonary edema, cardiac pain, or edema of the ankles. Of those not resubmitted, 211 (26.2 per cent) stated that they had either a heart murmur, "heart disease," or high blood pressure; of those resubmitted, 59 (30.7 per

NEW YORK. TABLE III

HISTORY AND CLINICAL EXAMINATION

DETAILS OF HISTORY AND EXAMINATION	TOTAL CASES EXAMINED	RESUBMITTED		NOT RESUBMITTED	
		NUMBER	PERCENTAGE	NUMBER	PERCENTAGE
TOTAL CASES	1000	192	100.0	808	100.0
Symptoms not present	679	188	97.9	491	60.8
Symptoms present	321	4	2.1	317	39.2
HISTORY					
Rheumatic fever over 5 years ago	284	36	18.8	248	30.7
within 5 years	46	1	0.5	45	5.6
Chorea over 5 years ago	41	3	1.6	38	4.7
within 5 years	0	0	0	0	0
Paroxysmal tachycardia	14	1	0.5	13	1.6
Paroxysmal auricular fibrillation	1			1	0.1
Murmur	105	33	17.2	72	8.9
Heart disease	115	16	8.3	99	12.3
Hypertension	50	10	5.2	40	5.0
Other	5			5	0.6
CLINICAL EXAMINATION					
Hypertension, transient	57	47	24.5	10	1.2
persistent, of nervous origin	8	8	4.2		
Tachycardia, transient	48	34	17.7	14	1.7
persistent, of nervous origin	6	6	3.1		
Apical systolic murmur, unexplained	99	99	51.6		
Aortic systolic murmur, unexplained	5	5	2.6		
Extracardiac murmur or click	3	3	1.6		
Cyanosis	6			6	0.7
Clubbing of fingers	4			4	0.5

cent) had this history. Symptoms were absent in 97.9 per cent of those resubmitted and in 60.8 per cent of those not resubmitted.

In the group of 545 cases with a final diagnosis of rheumatic valvular disease, 294 (53.9 per cent) gave a history of rheumatic fever or chorea. Rheumatic fever alone had occurred in 257 (47.1 per cent); chorea alone in 24 (4.4 per cent). The relative infrequency of antecedent chorea is striking. A history of both rheumatic fever and chorea was obtained in only 13 cases (2.4 per cent).

Of the total number examined, 284 stated that they had rheumatic fever more than five years ago, and 46 said that they had it within five years. In 41, there was a history of chorea more than five years ago; in no instance was there a history of chorea within five years. Of those resubmitted, 18.8 per cent said that they had rheumatic fever over five years ago, as compared to 30.7 per cent in those not resubmitted; of those resubmitted, 1.6 per cent had chorea more than five years ago, as contrasted with 4.7 per cent in those who were not resubmitted.

A history of paroxysmal tachycardia was obtained in fourteen of the total number and of paroxysmal auricular fibrillation in one. One man with a history of paroxysmal tachycardia was resubmitted because no substantiation of his story could be obtained and his account of the alleged attacks was not characteristic.

Transient hypertension was observed in 57 cases. Forty-seven of these, together with eight in which hypertension, though persistent, was regarded as of nervous origin, were resubmitted. In the ten showing transient hypertension who were rejected, some other disqualifying condition was present. Transient tachycardia was observed in 48 cases and persistent tachycardia, believed to be of nervous origin, in six. Fourteen of those with transient tachycardia were rejected for some other cardiovascular condition.

An apical systolic murmur of unexplained cause was present in 99 cases, an aortic systolic murmur of unexplained cause was observed in five cases, and in three an extracardiac murmur or click was heard; all were resubmitted. Murmurs at the apex or aortic area which, in the opinion of the examiners, were not due to organic cardiac disease were designated as "unexplained" rather than as functional, physiologic, accidental, or hemic, because the mechanism by which they are produced, as well as their significance, is unknown.

Among the cases of congenital heart disease, cyanosis was observed six times and clubbing of the fingers four times.

New York. Table IV

X-Ray and Electrocardiographic Examinations

FINDINGS	TOTAL CASES EXAMINED	RESUBMITTED		NOT RESUBMITTED	
		NUMBER	PERCENTAGE*	NUMBER	PERCENTAGE*
TOTAL CASES	1000	192		808	
X-RAY					
Not done	709			709	
Total cases done	291	192	100.0	99	100.0
enlargement	69			69	69.7
no enlargement	222	192	100.0	30	30.3
abnormal contour of heart	24			24	24.2
dilated aorta	1			1	1.0
question of tuberculosis	1			1	1.0
ELECTROCARDIOGRAM					
Not done	710	1		709	
Total cases done	290	191	100.0	99	100.0
normal	259	191	100.0	68	68.7
abnormal†	31			31	31.3

*In this case, percentage of cases done by each method of examination.
†For types of abnormality see Table V.

4. *X-ray and Electrocardiographic Examinations* (Table IV).—Two meter films of the heart were taken in 291 cases in which the clinical diagnosis was in doubt. Enlargement of the heart was present in 69; also, 24 showed an abnormal cardiac contour. In one instance, dilatation of the aorta was discovered. In another there were changes suggestive of active tuberculous lesions; this man also had signs of cardiac disease.

Electrocardiograms were done in 290 cases. The record was normal in 259 and abnormal in 31.

NEW YORK. TABLE V

ANALYSIS OF ABNORMAL ELECTROCARDIOGRAMS

TYPES OF ABNORMALITY	PHYSICAL SIGNS OF CARDIOVASCULAR DISEASE	
	NONE	DOUBTFUL
TOTAL CASES	5	26
Bundle branch block (QRS over 0.10 sec.)	3	3
Significant T wave negativity	1	4
T waves low (less than 1 mm. in limb leads)		1
Significant RS-T deviation		2
Q waves large (Leads I and IVF)	1	2
Blocked auricular premature beats		1
Heart block—incomplete (long P-R)		3
Axis deviation, left		6
Axis deviation, right		2
Broad, notched P waves		1
Marked notching of QRS		1
ECG only sign of disease	5	
Final diagnoses in cases in which ECG was abnormal		
Valvular heart disease, rheumatic	19	
Myocarditis, rheumatic (inactive)	1	
Enlargement of heart, etiology undetermined	4	
Congenital heart disease	2	

5. *Analysis of Abnormal Electrocardiograms* (Table V).—In five of the 31 cases the abnormality of the electrocardiogram was the only sign of cardiac disease and was considered of sufficient importance to justify rejection. In three of these, incomplete bundle branch block was observed, with QRS over 0.10 second. In one case with no history of cardiac disease and with a systolic murmur at the apex regarded as cardiorespiratory in origin, the electrocardiogram showed a sharply inverted T wave in Lead IVF. The x-ray revealed no cardiac enlargement. This case was rejected and the final diagnosis was given as "cardiac disease, type unspecified." In another case with neither history nor signs of cardiac disease, and with no enlargement in the teleroentgenogram, the electrocardiogram showed large Q waves in Leads I and IVF, together with left axis deviation. The Q wave in the precordial lead measured almost 5 mm. This man was not resubmitted. The occurrence of deep S waves, without other changes, was considered to be within the normal range.

In the remaining 26 cases, the physical signs were doubtful. In 19 the final diagnosis, after correlating the clinical features and the electrocardiogram, was rheumatic valvular heart disease; in one it was inactive rheumatic myocarditis; in four, on the basis of the x-ray, it was enlargement of the heart of undetermined etiology; and in two the abnormal electrocardiogram was regarded as confirmatory evidence of congenital heart disease, which had been suspected.

6. *Final Diagnoses* (Table VI).—No cardiovascular disease was found in 192 cases (19.2 per cent) and this was the group which was resub-

New York. Table VI

Final Diagnoses

DIAGNOSES	NO. OF CASES		PERCENTAGE OF CASES NOT RESUBMITTED	
TOTAL CASES	1000			
No cardiovascular disease—cases resubmitted	192			
CASES NOT RESUBMITTED	808		100.0	
Hypertension	159		19.7	
Tachycardia	48		5.9	
Rheumatic valvular disease—total	545		67.4	
mitral regurgitation		190		23.5
mitral stenosis		157		19.4
aortic regurgitation		35		4.3
aortic stenosis		3		0.4
combined mitral and aortic		160		19.8
Syphilitic aortitis and aortic regurgitation	4		0.5	
Suspected syphilitic aortic disease	3		0.4	
Congenital heart disease—total	30		3.7	
patent ductus arteriosus		7		0.9
defect of I-V septum		12		1.5
patent ductus and defect of I-V septum		4		0.5
subaortic stenosis		1		0.1
tetralogy of Fallot		1		0.1
dextrocardia		1		0.1
coarctation of aorta		1		0.1
type not specified		3		0.4
Cardiac enlargement—total	474		58.7	
due to disease specified		454		56.2
etiology undetermined		20		2.5
Myocarditis, rheumatic (inactive)	5		0.6	
External carotid aneurysm	1		0.1	
Coronary sclerosis	2		0.2	
Myocardial infarct, healed	1		0.1	
Neurocirculatory asthenia	31		3.8	
Heart disease due to chest deformity	5		0.6	
Hyperthyroidism	1		0.1	
Thrombophlebitis (inactive)	1		0.1	
Auricular fibrillation, permanent	11		1.4	
Auricular fibrillation, paroxysmal	2		0.2	
Paroxysmal tachycardia	5		0.6	
Extrasystoles (coupled rhythm)	1		0.1	
Bundle branch block	5		0.6	
Diagnosis unspecified	1		0.1	
Rejection and final diagnosis agree	639		79.1	
Rejection and final diagnosis disagree—total	280		-	
cases resubmitted		192		-
cases not resubmitted		88		10.9
Rejection diagnosis incomplete, comparison impossible	81		10.0	

mitted. Of the 808 cases not resubmitted, by far the commonest diagnosis was valvular heart disease of rheumatic etiology. This group comprised 545 cases, or 67.4 per cent. Next in the order of frequency was hypertension, with 159 cases (19.7 per cent). Then, in sequence, came tachycardia, neurocirculatory asthenia, congenital heart disease, and cardiac enlargement of undetermined etiology. Cardiac enlargement due to the disease specified in the diagnosis was present in 454 cases, or 56.2 per cent of the total number.

In the rheumatic group, mitral regurgitation alone was found 190 times and combined mitral and aortic disease 160 times. Mitral stenosis was present in 157 cases and aortic regurgitation in 35. Syphilitic aortitis with aortic regurgitation was observed only four times; in three cases syphilitic aortic disease was suspected. All of the seven cases of aortic syphilis, proved or suspected, were found in Negroes.

Of the thirty cases of congenital heart disease, twelve were considered to be due to a defect of the interventricular septum, and seven to patent ductus arteriosus. In four, these two defects were combined. There was one instance each of subaortic stenosis, tetralogy of Fallot, dextrocardia, and coarctation of the aorta. In three cases the type of congenital defect could not be determined with accuracy and was not specified.

It is perhaps of interest to note that the following conditions were encountered: aneurysm of the external carotid artery, once; coronary sclerosis, twice; healed infarct of the myocardium, once; heart disease due to chest deformity, five times. Permanent auricular fibrillation was observed in eleven cases; all had rheumatic valvular disease.

In 639 cases (79.1 per cent), the original rejection diagnosis and the final diagnosis were in agreement; in 10.9 per cent they were in disagreement; and in 10 per cent comparison was impossible because of the incompleteness of the original record furnished by the local board. Some of the original rejection diagnoses and the final diagnoses replacing them are here given:

Original	*Final*
Valvular heart disease, rheumatic	No cardiovascular disease Hypertension Congenital heart disease Neurocirculatory asthenia
Congenital heart disease	Rheumatic valvular disease
Hypertension	No cardiovascular disease Neurocirculatory asthenia Rheumatic valvular disease Cardiac enlargement—etiology unspecified
Tachycardia	No cardiovascular disease Rheumatic valvular disease Hypertension Neurocirculatory asthenia
Neurocirculatory asthenia	Tachycardia Cardiac enlargement
Cardiac hypertrophy	No cardiovascular disease Rheumatic valvular disease

7. *Basis of Rejection in Cases Not Resubmitted* (Table VII).—Of the 808 cases not resubmitted, 733 were rejected on the basis of the clinical examination alone, and 75 with the aid of the x-ray or electrocardiogram.

NEW YORK. TABLE VII

BASIS OF REJECTION IN CASES NOT RESUBMITTED

	NUMBER OF CASES		PERCENTAGE OF TOTAL CASES	
TOTAL CASES REJECTED	808		100.0	
Rejected on clinical examination alone	733		90.7	
Rejected with aid of x-ray or electrocardiogram	75		9.3	
X-ray decisive		49		6.1
Electrocardiogram decisive		14		1.7
X-ray and electrocardiogram both decisive		12		1.5

Of the 75, 49 were rejected because of cardiac enlargement found on x-ray examination; 14 because the electrocardiogram was either the only abnormality or confirmed doubtful clinical signs; and 12 because both the x-ray and the electrocardiogram were abnormal.

SUMMARY AND CONCLUSIONS

1. In New York City, 1,000 registrants for the Draft, who had been rejected for military service because of cardiovascular defects, were re-examined by a Special Medical Advisory Board. These men had been *rejected by local boards or induction stations.* Of the total number, 192 (19.2 per cent) were considered not to have cardiovascular disease. By arrangement with Selective Service and the Army, it was agreed that these men should be resubmitted to an induction station, and it was recommended that they be placed in Class 1A and accepted for duty. Their records are to be made available after the war, so that a follow-up study may be undertaken.

2. The plan of procedure during these examinations has been outlined and the criteria for rejection have been described.

3. Rheumatic valvular heart disease was by far the commonest cause of disability (67.4 per cent of the total number finally rejected). Next in order came hypertension, persistent tachycardia, neurocirculatory asthenia, and congenital heart disease. Cardiac hypertrophy of undetermined etiology was found with surprising frequency, namely, in twenty cases.

4. The original rejection diagnosis and the final diagnosis made after re-examination were in agreement in 79.1 per cent of 808 cases not resubmitted.

5. The 2 meter film of the chest was of great value in estimating the size of the heart. In 49 cases it was the decisive factor in furnishing the basis for rejection; in another 12 cases it showed cardiac enlargement when the electrocardiogram likewise was abnormal.

6. The electrocardiogram alone furnished a basis for rejection in only five cases. It was found abnormal in another 26 in which the physical signs were doubtful; in 12 of these cardiac enlargement was discovered in the x-ray film.

7. The occurrence of a systolic murmur at the apex furnished the most difficult problem in diagnosis. A history of rheumatic fever, the intensity of the murmur, the extent of its transmission and its modification by posture and respiration were all factors aiding in the decision as to whether the murmur was indicative of organic disease of the mitral valve. However, judgment was difficult and the accuracy of the final decision is open to question. Only by following a large group of these individuals over a period of years can a true appraisal of the importance of such murmurs be made.

8. The critical levels of systolic and diastolic blood pressures likewise have not been established on a firm basis. Speculation on the basis of present evidence is unfruitful. Until further data are available or until the need for man power becomes acute, it would seem wise to adhere to the criteria at present in use, both because of possible future damage to the individual and because of the danger of swelling the pension lists for disability.

9. The range of the normal heart rate is perhaps subject to a more liberal interpretation. Tachycardia is readily induced by slight emotion and, if unaccompanied by hypertension, probably puts less strain on the circulation than does an increase in blood pressure, particularly when the diastolic level is elevated. Consideration should be given to raising the critical level of the heart rate; it is suggested that if this does not exceed 120 per minute the registrant be accepted.

10. It is worth noting that in the series of fourteen examination periods during which this study was made, there was a gradual tendency to be more liberal in the interpretation of doubtful signs; this attitude applied especially to the apical systolic murmur. At the first session only 13.5 per cent of those examined were resubmitted; at the final session 27.2 per cent of those examined were resubmitted. The trend was gradually upward, though not in an unbroken line.

11. The actual number of men salvaged was relatively small; the labor and expense were considerable. For these reasons, it does not seem feasible or necessary at this time to recommend extension of the work. Yet this survey will not have been made without profit. It has demonstrated the possibility of rejecting a smaller number for cardiovascular defects. It is hoped that it has defined more clearly the criteria for rejection by making them more specific and objective. It has indicated the need for further study of the meaning of certain physical signs, particularly the systolic murmur. It has emphasized the desirability of knowing more concerning the range of normal blood pressure and heart rate. By following the group resubmitted, both in this city and in the others in which similar observations have been made, information should be obtained which will prove useful, not only during war, but in times of peace.

Selective Service, New York City Headquarters
1 East 44th Street, New York City

Hon. Thomas E. Dewey, Governor
Brig. Gen. Ames T. Brown
The Adjutant General, State Director
Col. Arthur V. McDermott
New York City Director

Refer to File: SJK:A January 26, 1943.

To: Chairman of Local Board #----------
Subject:—Re-Examination of Rejected Heart Cases.

1. Under a project of the National Research Council there has been set up in the New York City Area, a special Medical Advisory Board of expert Heart Specialists.

2. These experts are directed to examine registrants rejected for heart disease. The Directive from National Headquarters reads as follows:

> ''It is desirable to select ambulant cardiovascular rejectees, exclusive of any rejected because of hemorrhoids or varicose veins, but *including* those rejected for neurocirculatory asthenia, paroxysmal tachycardia, and past and present rheumatic fever.
>
> ''Cardiovascular cases bedridden and invalided, or those with other concomitant conditions which would cause their rejection *will not be forwarded.*
>
> ''It is expected that D.S.S. Form 1003 will be made out in *sextuplicate.* The local board clerk should *fill in Section I* of the original and all copies of this form and present them *with* the registrant. Any papers pertaining to former physical examinations, x-ray films, or electrocardiograms in this registrant's cover sheet which *may be pertinent* to this *cardiovascular* examination will also be made available to the (special) Medical Advisory Board.''

s/s C. G. Parker, Jr., Colonel, U. S. Marine Corps
Deputy Director

3. The above is being passed on to you for your attention and compliance. Herewith are a number of Forms 1003.

4. Appended are the order numbers of registrants in your Board which the files at this Headquarters list as proper to send to this special Medical Advisory Board.

5. The examinations will be held at the Presbyterian Hospital, 622 West 168th Street, New York City. The examinations will be under the immediate charge of Dr. Robert L. Levy, and will be held for those of your Board on ---------------, 1943, at -------------- o'clock.

The following order numbers of registrants of your Board have been selected from our record-files as suitable for submission to this special examination. If for any reason you cannot forward any particular one of the registrants whose order number is listed below, you are at liberty to substitute another whose rejection for heart disease is in your IV-F file. If substitutes are submitted, please send me their order numbers.

The order numbers you are to submit are:

Thank you for your cooperation.

For the New York City Director,
Samuel J. Kopetzky, Colonel, M. C., Medical Division

ADDENDUM

FOLLOW-UP OF 192 MEN RESUBMITTED AFTER RE-EXAMINATION BY THE NEW YORK BOARD, AS OF FEBRUARY 11, 1944

Accepted for Service (total)		140
Army	110	
Navy	27	
Marine Corps	3	

Of the 110 accepted by the Army, two were subsequently discharged for physical disability with the diagnosis of "Valvular Heart Diseases, Mitral Stenosis and Insufficiency. Existed Prior to Induction."

Fifteen who were resubmitted were placed in the following "Deferred Classifications":

1-A-H	1
2-A	3
2-B	10
3-A	2
3-D	1

Thirty-seven who were resubmitted were again rejected, 34 by the Induction Station and 3 by the local board physician. The causes for rejection were:

Cardiovascular (total)		2
Hypertension	1	
Tachycardia	1	
Other (total)		35
Neuropsychiatric reasons	14	
Tuberculosis, pulmonary	5	
Hernia	5	
Defective vision	4	
Orthopedic defect	2	
Administrative reasons	2	
Hemorrhoids (ulcerated)	1	
Duodenal ulcer	1	
Undescended testicle	1	

REPORT OF THE PHILADELPHIA BOARD

WILLIAM D. STROUD, M.D., CHAIRMAN

PERSONNEL

Cardiovascular Examiners:

Samuel Bellet
George C. Griffith
Thomas M. McMillan
George Morris Piersol
William D. Stroud, Chairman

Roentgenologist: Paul A. Bishop

Nurse in Charge: Myra Cassel

Secretarial Group:

Ruth Bruder
Helen Clapp
Grace Martin
Dolores Roberts
Caroline Wittman
Esther Greenburg
Catheryn Grundy
Florida Murphy

Electrocardiographic Technicians:

Catharine B. Sutterley
Margaret G. McCusker

Roentgenologic Technicians:

Selena Black
Isabel Gerber

THE examination of men rejected for cardiovascular disease either by the local examining boards or the Induction Center in Philadelphia was carried on in the Out-Patient Department, at the Pennsylvania Hospital, from January 26 to March 23, 1943. The examinations were made on Tuesday and Friday evenings from 6:30 until 9:30 P.M. There were in all a total of eighteen sessions, with an average of about 58 examined per evening.

The doctors who participated in the examination were members of a Medical Advisory Board (Cardiologic) appointed by the Governor of the State of Pennsylvania, at the request of Lt. Col. B. F. Evans, Acting Director of Selective Service in Pennsylvania. This Board consisted of Drs. Samuel Bellet, George C. Griffith, Thomas M. McMillan, George Morris Piersol, and William D. Stroud, Chairman.

The selection of cases, and the successful arrangement whereby the men were sent by the local boards to the hospital for examination, was almost entirely due to the work of Lt. Col. Edgar S. Everhart, Medical

Officer, Selective Service System, Pennsylvania. Colonel Everhart attended the first session in order to see that things ran smoothly.

The rejectees were sent from 33 local boards in the central part of Philadelphia. This meant that there were quite a large number of men with Italian parentage and a total of 207 (20 per cent) Negroes among the 1,035 men examined.

The men were selected by the local boards by order number, with the supervision of a physician on the board. The local board records were sent to the Pennsylvania Hospital previous to the evening on which each man was to be examined. Upon arriving at the Out-Patient Department, the rejectees were weighed and their heights were taken. Each man was then examined while recumbent, by a member of the Board. If the examiner felt the diagnosis on the rejectee's Form DSS 221 was correct, the special form No. 1003, supplied by Selective Service Headquarters in Washington, was not completely filled out, but a complete diagnosis was made. If the examiner felt the rejectee should be reclassified as 1A, Form 1003 was completely filled out, electrocardiogram and 2 meter films were made, and, if the results were within normal limits, a diagnosis of no organic heart disease was made after consultation with either Dr. McMillan or Dr. Stroud.

As a result, 171 cases with the original diagnosis of the local board or induction center were recommended for reclassification as 1A (see Table I at end of paper).

In the case of 864 men, the examiners agreed with the previous diagnosis and recommended rejection for active service (see Table II).

CRITERIA EMPLOYED

The requirements of Mobilization Regulations No. 1 to 9, by the War Department, Washington, Oct. 15, 1942, Sections 60 to 67, were fulfilled.

A pulse rate of 100 or over, after thirty minutes rest on a bed in a quiet room, was considered disqualifying. It was the opinion of the members of the Board, however, that probably this limit should be raised if all other findings are within normal limits. A blood pressure persistently above 150/90 was considered disqualifying also.

Strangely enough, in the 174 men considered clinically worthy of reclassification as 1A, only three definitely abnormal electrocardiograms were found. Two of these had negative T_1, T_2, and T_3, and one had negative T_2 and T_3, all having had the tracings taken in both the sitting and recumbent positions. In spite of the negative clinical findings, these cases were not recommended for reclassification as 1A. A number had left axis deviation, which was considered due to the individual's build, and a number had multiple premature contractions, which were not considered disqualifying. Electrocardiograms were done only on those clinically recommended for reclassification.

Dr. Paul A. Bishop, the Roentgenologist at the Pennsylvania Hospital, devoted a great deal of time to studying the 2 meter films of those considered clinically to have normal hearts. He found 45 of the rejectees with transverse cardiac diameters of 1 cm. or more above the predicted normal for their height, weight, and age, according to the table of Hodges and Eyster. After carefully going over the clinical picture and the films of these cases with members of the Medical Advisory Board, he agreed that, of the 45, only nine had sufficient x-ray evidence of cardiac enlargement to cause rejection.

RESULTS

The two most difficult problems were a systolic murmur at the cardiac apex and increased heart rates with blood pressures slightly above normal. Many men originally classed as 4F had only a systolic murmur in the pulmonic region, which was considered functional. Of the 160 men rejected for mitral insufficiency without cardiac enlargement, a great many, we believe, did not have organic valvular heart disease, but the loudness of the murmur in certain positions and following exercise caused rejection, because of the possibility that, if reclassified, they would be discharged from the Service sooner or later.

It is interesting to note that by far the majority of cases not recommended for reclassification had rheumatic heart disease—569 men, or 66 per cent. Two hundred men, or 23 per cent, had arterial hypertension, and 54 men, or 6.2 per cent, had neurocirculatory asthenia.

Of the 1,035 men examined, 207, or 20 per cent, were Negroes. Of these, 33, or 16 per cent, were recommended for reclassification as 1A. Of the 569 men with rheumatic heart disease, 111, or 19.5 per cent, were Negroes. Of the 200 men with arterial hypertension, 54, or 27 per cent, were Negroes. It is interesting how few cases of neurocirculatory asthenia were observed in Negroes, namely, 2, or 3.8 per cent, out of a total of 54 of such cases.

We were much surprised to find how seldom a positive history of rheumatic fever was obtained in cases with definite rheumatic heart disease. Of 569 such cases, only 89 (15.6 per cent) gave a history of rheumatic fever, and only 4 (0.7 per cent) a history of chorea.

Appended are three letters from members of the Board, outlining their reactions to the study. They are worth reading carefully.

In closing, I cannot help thanking all of those who participated in this study for their cheerful cooperation and hard work. It was a long, and at times a tiresome, job, but I believe that the results have been worth while.

LETTERS FROM EXAMINERS

Dear Dr. Stroud:

Regarding the re-examination of rejectees the following thoughts come to mind:

The causes for rejection of selectees are subdivided under the following headings:

Murmurs.—The great majority rejected because of valvular disease were found to have organic murmurs at the apex or base, or both. The remainder who were considered acceptable for service showed the following findings.

a. No murmurs.

b. Systolic murmurs at the pulmonic region which were considered functional. These had been labeled as organic of the acquired or congenital type.

c. Systolic murmurs at apex—Grade I (definitely functional).

d. Systolic murmurs at the aortic area.

In many, a systolic murmur was produced, or, if previously present, was exaggerated, by tachycardia and/or hypertension.

The large single group in which doubt arose were those with Grade II systolic apical murmurs, who gave no history of rheumatic infection, had no symptoms referable to the cardiovascular system, and showed a heart normal in size and shape upon roentgen study. Many of these, we believe, had no endocardial lesion and could be acceptable for service. They were able, in many instances, to work at an occupation involving strenuous physical effort without symptoms.

Hypertension.—Most of those rejected for hypertension showed hypertension. Those of this group considered acceptable presented:

a. No hypertension on our examination.

b. A rise in blood pressure to 160 or 170 mm. which dropped to normal upon resting in bed for 10 to 20 minutes. The hypertension in these cases was considered to be of psychic origin.

The remainder showed blood pressure readings of 160 mm. and over, which persisted after a thirty-minute rest and were associated, in many instances, with a tachycardia, cardiac enlargement, and a Grade II systolic apical murmur.

The hypertensive group is important, not only because of its size but because it is frequently a transient manifestation of anxiety and may be produced by malingerers. Considerable care and investigation are required before rejection of these cases. I mention the following as illustrative: Last week I examined a young man of 32 years who had been rejected at the Induction Center because of high blood pressure; he had had two readings of 160 and 190 mm.; at my office he had a blood pressure of 140 mm., and showed a heart that was entirely normal.

In this connection it might be stated that the environmental conditions for examining hypertensives at the Induction Board at 32d and Lancaster Avenue are not particularly good. There are no separate rooms and people are constantly milling about. The selectees are usually under severe nervous strain at the time of the examination; many have spent sleepless nights before this event, and others have engaged in various types of dissipation and have imbibed large amounts of coffee and other stimulants. These are all factors in raising the blood pressure and should be discounted in determining the basal status of the individual selectee.

Tachycardia.—Simple tachycardia, with rate over 100 per minute, was frequently encountered. This group may be divided into several categories:

a. Where the patients normally have a high pulse rate (a small group).

b. Where the acceleration is the result of nervousness and worry and may be considered part of an anxiety state.

c. Mild grade of hyperthyroidism.

d. Where the acceleration was the result of additional factors which may border on malingering, due to factors similar to those mentioned under hypertension.

The possible use of benzedrine and other sympathetic stimulating drugs should be ruled out.

Cases in which the pulse rate exceeds 110 per minute under conditions which are considered basal should be rejected.

Comment.—After perusal of the various reports from different parts of the country, it might be desirable to establish new criteria for acceptance of cardiacs,

at least to define more clearly the borderline groups. Based on these, it might be of interest to repeat this study in other parts of the country.

These standards might be also utilized by draft board physicians for future cardiac evaluations.

SAMUEL BELLET

Dear Dr. Stroud:

In re the re-examination of rejectees, the following thoughts come to mind:

1. This Medical Advisory Board's examination of rejected cardiovascular subjects was of value to the rejected selectee, because it answered any doubt which he might have in mind regarding his disability.

2. It was of value to the Selective Service, because it restored to the Selective Service approximately 17 per cent of the men examined, making them available for active military duty.

3. Examinations were of value to the physicians composing the Advisory Board, because they called for the necessity of making a definite decision with the aid of exceedingly well-trained colleagues.

4. Examinations were of great value to the medical profession, and an opportunity for real study should be called to the attention of the American Medical Association, the College of Physicians, the American Heart Association, and local heart associations.

5. The study should prove of real value to the Rehabilitation Committee, who should use this data for war and postwar planning for extended rehabilitation.

GEORGE C. GRIFFITH.

Dear Dr. Stroud:

In re the re-examination of cardiovascular rejectees, the following thoughts come to mind:

I believe that the final tabulation showed that we recommended for re-examination some 20 per cent of the 1000 rejectees examined.

It is my feeling that if these 1000 young men had been examined in our offices as civilians, we probably would have decided that at least 60 per cent had no organic circulatory disease. It was my feeling that a considerable percentage of those rejected had no organic cardiovascular disease. However, there is good reason for this discrepancy, and, in my opinion, we would have made a mistake had we sent back for re-examination many more than we did return.

In this sort of work I think it is necessary to set up certain standards and to adhere to them. For, after all, we were not the last word; we had no authority to do more than recommend a re-examination. We would have erred, therefore, in returning persons who showed certain findings which subsequent examiners would regard as cause for rejection even though we, as specialists, felt that these findings were unimportant. In other words, we should not use our special knowledge and experience too finely, and should not apply it beyond the point which subsequent examiners can readily accept.

Murmurs were, as ever, a source of difficulty. In deciding to reject any one who showed a definite apical systolic murmur, I think we acted properly, though many so rejected did not, in my opinion, have organic heart disease. I think it was also a sound decision to accept murmurs (1) that were heard at the aortic area, but were soft; (2) that were not heard in all phases of respiration; (3) that clearly originated at the pulmonic area; (4) that were late in systole and soft, even if they were best heard at the apex. I believe subsequent examiners will find it possible to accept and follow these criteria.

Many that were rejected for mild hypertension or for a rapid heart rate certainly had no organic circulatory disease. However, after my experiences with

neurocirculatory asthenia in France in the last war, I am of the opinion that those whose blood pressure goes above 160 or whose pulse rate reaches 120, as a result of the excitement incident to an examination, and which do not return to normal after a half hour's rest in the prone position in quiet surroundings, are not good candidates for the Army. I think, incidentally, that a heart rate of 100 is a little too low. I would be inclined to raise it to 110 or even 120 before considering this a cause for automatic rejection.

THOMAS M. MCMILLAN

PHILADELPHIA. TABLE I

REJECTEES RECOMMENDED FOR RECLASSIFICATION AS 1A

DIAGNOSIS OF LOCAL BOARD OR INDUCTION CENTER	TOTAL (NO.)	TOTAL (%)	WHITE (NO.)	WHITE (%)	NEGRO (NO.)	NEGRO (%)
Valvular heart disease	97	56.7	77	79.4	20	20.6
Arterial hypertension	33	19.3	25	75.8	8	24.2
Tachycardia	14	8.2	13	92.9	1	7.1
Cardiac enlargement	5	2.9	5	100.0		
Heart condition	12	7.0	9	75.0	3	25.0
Neurocirculatory asthenia	4	2.3	3	75.0	1	25.0
Cardiac arrhythmia	2	1.2	2	100.0		
Hyperthyroidism	1	0.6	1	100.0		
Presence of rheumatic fever	1	0.6	1	100.0		
Congenital heart disease	1	0.6	1	100.0		
Psychoneurosis	1	0.6	1	100.0		
Total	171	16.5	138	80.7	33	19.3

PHILADELPHIA. TABLE II

REJECTEES NOT RECOMMENDED FOR RECLASSIFICATION

DIAGNOSIS OF MEDICAL ADVISORY BOARD (CARDIOLOGIC)	TOTAL (NO.)	TOTAL (%)	WHITE (NO.)	WHITE (%)	NEGRO (NO.)	NEGRO (%)
Rheumatic heart disease						
Mitral insufficiency	160		134		26	
Mitral insufficiency (C.E.)*	148		100		48	
Mitral stenosis	131		115		16	
Aortic insufficiency	4		1		3	
Aortic insufficiency and mitral insufficiency	37		28		9	
Aortic insufficiency and mitral stenosis	54		49		5	
Aortic stenosis and mitral insufficiency	16		12		4	
Aortic stenosis and mitral stenosis	19		19			
Total rheumatic heart disease	569	65.9	458	80.5	111	19.5
Hypertension—arterial	200	23.1	146	73.0	54	27.0
Neurocirculatory asthenia	54	6.2	52	96.2	2	3.8
Congenital heart disease; pulmonary stenosis	9	1.0	7	77.8	2	22.2
Congenital heart disease; patent ductus arteriosus	4	0.5	4	100.0		
Congenital heart disease; patent ductus arteriosus; pulmonary stenosis	1	0.1	1	100.0		
Congenital heart disease; patent interventricular septal defect	4	0.5	1	25.0	3	75.0
Syphilitic heart disease; aortitis	2	0.2			2	100.0
Syphilitic aortic insufficiency	1	0.1	1	100.0		
Tachycardia	8	0.9	8	100.0		
Rejected on x-ray alone	9	1.0	9	100.0		
Rejected on electrocardiogram alone	3	0.3	3	100.0		
Total	864	83.5	690	79.8	174	20.2

*C.E. = Cardiac enlargement.

PHILADELPHIA. TABLE III

RESULT OF RE-EXAMINATION BY SPECIAL BOARD

Total number examined	1,035
Number resubmitted	171
Number rejected	864

PHILADELPHIA. TABLE IV

ORIGINAL REJECTION DIAGNOSES

(By Local Board or Induction Station)

DIAGNOSES	NUMBER FINALLY RESUBMITTED	NUMBER FINALLY REJECTED
Rheumatic valvular heart disease	97	550
Hypertension	33	227
Tachycardia	14	35
Congenital heart disease	1	10
Cardiac hypertrophy	5	5
Rheumatic fever—recent	1	1
Heart disease—unspecified	12	26
Neurocirculatory asthenia	4	3
Cardiac arrhythmia	2	1
Cardiac neurosis	1	
Syphilis of aorta		3
Aneurysm of aorta		
Aneurysm, other than aortic		
Heart disease due to chest deformity		
Coronary heart disease		
ECG abnormality only		
Peripheral vascular disease		
Pericarditis		
Nephritis (persistent albuminuria)		2
Hyperthyroidism	1	1
Total	171	864

PHILADELPHIA. TABLE V

FINAL REJECTION DIAGNOSES IN CASES NOT RESUBMITTED BY SPECIAL BOARD

Rheumatic valvular heart disease	569
Hypertension	200
Tachycardia	8
Congenital heart disease	18
Syphilis of aorta	3
Aneurysm of aorta	0
Aneurysm other than aortic	0
Cardiac enlargement only	9
Myocarditis, rheumatic	0
Coronary heart disease	0
Heart disease, unspecified	0
Neurocirculatory asthenia	54
Auricular fibrillation—paroxysmal	0
Auricular fibrillation—permanent	9
Paroxysmal tachycardia	0
Cardiac arrhythmia only	0
Cardiac neurosis	0
Recent rheumatic fever	0
Pericarditis	0
Heart disease due to chest deformity	0
ECG abnormality only	3
Peripheral vascular disease	0
Nephritis (persistent albuminuria)	0
Hyperthyroidism	0

PHILADELPHIA. TABLE VI

TYPES OF RHEUMATIC VALVULAR HEART DISEASE IN REJECTED CASES

(Final diagnoses by Special Board)

Total number cases rheumatic valvular disease	569
Mitral regurgitation	308
Mitral stenosis	131
Aortic regurgitation	4
Aortic stenosis	0
Combined mitral and aortic	126

PHILADELPHIA. TABLE VII

HISTORY OF RHEUMATIC FEVER OR CHOREA IN CASES WITH VALVULAR HEART DISEASE

History of rheumatic fever	89
History of chorea	4
History of both rheumatic fever and chorea	0

PHILADELPHIA. TABLE VIII

TYPES OF CONGENITAL HEART DISEASE IN REJECTED CASES

(Final diagnoses by Special Board)

Patent ductus arteriosus	4
Defect of I-V septum	5
Defect of I-A septum	
Subaortic stenosis	
Tetralogy of Fallot	
Coarctation of aorta	
Pulmonic stenosis	9
Dextrocardia	
Low aorto-pulmonary artery communication	
Prominent pulmonary artery	
Combined lesions	
Patent ductus and I-V septal defect	
Patent ductus and pulmonic stenosis	1
Patent ductus and dextrocardia	
Defect of I-V septum and coarctation of aorta	
Unspecified	

PHILADELPHIA. TABLE IX

DISTRIBUTION OF CERTAIN FINAL DIAGNOSES BY RACE

(No Chinese or Filipinos were examined)

	WHITE	NEGRO
Total number examined	828	207
Number resubmitted	138	33
Number rejected	690	174
Rheumatic valvular disease	458	111
Hypertension	146	54
Tachycardia	8	0
Neurocirculatory asthenia	52	2
Congenital heart disease	13	5
Syphilis of aorta (incl. aneurysm)	1	2
Coronary heart disease	0	0
Permanent auricular fibrillation	9	0
Paroxysmal tachycardia	0	0

PHILADELPHIA. TABLE X

MISCELLANEOUS DATA

No. of cases resubmitted with hypertension, believed to be of nervous origin	0
No. of cases resubmitted with tachycardia, believed to be of nervous origin	0
No. of cases resubmitted with unexplained (nonpathologic) apical systolic murmurs	21
No. of cases resubmitted with unexplained (nonpathologic) aortic systolic murmurs	0
No. of cases in which the ECG was the *deciding factor* in final rejection diagnosis (This does not necessarily mean it was the *only* finding, e.g., a systolic murmur also may have been present)	3
No. of cases in which x-ray of the chest was the *deciding factor* in final rejection diagnosis	9
No. of cases in which *original* rejection diagnosis (by local board or induction station) agreed with *final* rejection diagnosis of Special Board	602
No. of cases in which there was disagreement between original and final rejection diagnoses	262
No. of cases in which incomplete original diagnosis made *comparison* impossible	38
The three or more original rejection diagnoses with which the final diagnoses most frequently disagreed (in order of frequency of disagreement) 1. Valvular heart disease 2. Hypertension 3. Tachycardia	

ADDENDUM FOR PHILADELPHIA RE-EXAMINATION REPORT

Of the 171 rejectees recommended for resubmission for examination at the Induction Center as probable 1A, 107 were accepted for military service by Aug. 19, 1943. There were 44 rejected and 20 not re-examined, for other reasons. The causes for the second rejection were as follows:

Hypertension		5 cases
Patent ductus arteriosus		1 case
Valvular heart disease (mitral)		1 case
Heart block		1 case
Occlusion of left brachial artery		1 case
Nervous and mental		14 cases
Miscellaneous		21 cases
Otitis media	3	
Hernia	3	
Defective vision	3	
Albuminuria	1	
Alcoholism	1	
Asthma	1	
Bronchitis	1	
Fistula in ano	1	
Fracture	1	
Obesity	1	
Stricture	1	
Syphilis	1	
Tuberculosis	1	
Stammering	1	
Osteomyelitis	1	

REPORT OF THE SAN FRANCISCO BOARD

WILLIAM J. KERR, M.D., CHAIRMAN

ORGANIZATION

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Paul Gliebe (Psychiatry)
Mayo H. Soley (Neurocirculatory asthenia)
Earl R. Miller (Roentgenology)
Resident Staff and interns in Medicine and Roentgenology

Secretarial and Technical Staff:

Medicine
Elena Bogdanoff
Mary M. Ehlert
Frances L. Gutzman
Carol F. Higby
Eleanor Little
Mildred Perry
Sylvia Posner
Barbara Saunders
Mildred Truett

Electrocardiograph
Jean Hitch
Ola Nagle
Evelyn Tiernan

X-ray
Emily Bacon
Esther Ross
Ione Shrader
Ann Temple

Laboratory
Fermer Lloyd

HOUSING AND TIME FOR OBSERVATIONS

WAITING rooms and examining rooms in Out Patient Department of the University of California Hospital.

Time of sessions: Monday, Wednesday, and Friday evenings, 7 to 10, or until finished.

Fluoroscopic unit, electrocardiographic laboratory, and clinical laboratory. Out Patient Department of the University of California Hospital.

X-ray film rooms, University of California Hospital, adjacent to Out Patient Department.

ARRANGEMENTS FOR EXAMINATIONS

Through the California State Selective Service headquarters, Sacramento, California, instructions were issued to the local boards in the San Francisco City and County, to "pull" the records of all draftees in 4F who had been rejected for cardiovascular diseases and who showed no other rejectable defects. A sergeant was assigned to serve temporarily with our Special Board to facilitate the study. Subsequently, the local boards in Oakland and Berkeley were instructed to do likewise to secure the total of more than 1,000 suitable records.

At frequent intervals, and at least ten days before the dates for appointments to report for examination, the Chairman met with the sergeant to go over individual records to make sure that no men were called with (1) other rejectable defects, (2) positive serological tests for syphilis, or (3) those who would reach the age of 38 years within a month of the time of examination.

Groups of 50 to 55 were called for the earlier examinations; later, 60 to 70 were called when it became apparent that a larger number could be examined efficiently.

Some difficulty was experienced in completing the electrocardiograms and roentgenograms on the evening of the examinations because the doubtful conditions required longer study and many of these accumulated toward the end of the evening. To obviate a return visit it was frequently necessary to keep the technicians and some of the secretaries until a late hour.

The Resident Staff were of great assistance in making some of the preliminary examinations to conserve the time of the chief examiners, especially in those subjects with tachycardia and hypertension requiring many observations. Incidentally, the opportunity for these assistants to see such a large and varied collection of cardiovascular conditions was of great educational value.

At the beginning of each session, subjects were passed rapidly through the fluoroscopic unit and then placed at rest in the examining rooms. Each examiner had three or more quiet rooms which we found important for proper observation and to provide space for prolonged rest when required for subjects with tachycardia or hypertension.

Consultations between examiners were frequent, and in all cases where a chief examiner thought the candidate had a doubtful lesion or one which would place him in the 1A group, one or more examiners verified the findings of the first examiner.

From the beginning, we were anxious to make special observations on three groups of subjects. We were particularly interested in noting the number of subjects with coarctation of the aorta. Our high incidence of this condition, in comparison with the findings of the other units, is striking; perhaps due in part to the higher relative incidence of congenital lesions in this geographic area. We had associated with

us an able psychiatrist who made special observations on those with persistent tachycardia and persistent hypertension, and a physician skilled in physiologic methods who made special observations on subjects with suspected neurocirculatory asthenia.

Most of our subjects were of the white race. The figures for the Negro race are not immediately available but they constituted a negligible group for statistical purposes.

During the early part of the examinations the standards of acceptance were those specified by the Selective Service instructions MR 1-9. Following the receipt of a memorandum of decisions from the Boston Unit, February, 1943, we adopted a more liberal attitude concerning tachycardia and hypertension, namely, maximum levels of 110 for the pulse rate and 160/95 for blood pressure readings. We recalled all the borderline cases previously examined and accepted a number of those who would have been otherwise rejected.

A total of 983 subjects were examined. Of these, 24 were found to have no cardiovascular abnormality but had other defects which were specified for the benefit of the local draft boards. These clinical conditions are listed, and these 24 subjects have been counted in compiling our statistics, in view of the fact that they were originally rejected for cardiovascular disease where no rejectable cardiovascular disease was found to exist, and because we may have overlooked other rejectable noncardiovascular disease which may be found subsequently at induction centers.

RESULT OF THE EXAMINATIONS

The results of the examinations are tabulated as follows:

Total number examined	983	
Number accepted	275	= 28.0 per cent of total
Number accepted as to cardiovascular system but rejected for other defects	24	= 2.4+ per cent of total
Number rejected for cardiovascular defects	684	= 69.5+ per cent of total

A table showing comparative figures for draftees rejected by local boards and induction centers and results of our examinations includes 24 men accepted for cardiovascular status but rejected for other causes.

Rejected by local boards and medical advisory boards	420	
Accepted by our board	181	= 43.1 per cent
Rejected by induction centers	563	
Accepted by our board	117	= 20.78 per cent

The diagnoses of the specific clinical status of the entire group of 983 have been arranged alphabetically in Table II and the comparison of our findings with those of the local draft boards and the induction centers is shown.

The data of our examination have been arranged and grouped in Tables I, II, and III.

SAN FRANCISCO. TABLE I

	REJECT	ACCEPT
Syphilitic aortitis presumptive—positive history, negative serology test	2	
Valvular heart disease, all types	297	
Recent history of rheumatic fever	3	
Hypertension	202	
"Nervous hypertension"		31
Tachycardia	17	
"Nervous tachycardia"		19
Neurocirculatory asthenia	19	
Anxiety neurosis	6	
Angina pectoris	1	
Myocardial infarction	1	
Pericarditis	3	
Physiologic or functional murmurs		89
Systolic click		3
Congenital heart disease (total 60):		
Coarctation of the aorta	8	
I-V septal defect	25	
Patent ductus Botalli	9	
Pulmonary stenosis	1	
Interauricular septal defect	1	
Other congenital defects and mixed	16	
Enlargement of heart by x-ray beyond acceptable limit without other defects	26	
Thromboangiitis obliterans	2	
Heart displaced by pulmonary disease	1	
Funnel breast with displaced heart	2	
Poor training		2
Hyperthyroidism	1	
Nephritis	2	
Borderline cardiovascular disease, combination of clinical findings, x-ray, and electrocardiographic changes	8	
Disturbed mechanisms and arrhythmias:		
Auricular tachycardia (paroxysmal) chiefly on verified history	5	
Auricular flutter (secondary diagnosis)	1	
Auricular fibrillation	2	
A-V heart block	4	
Bundle branch block	2	
Sensitive carotid sinus	1	
Vagotonia	1	
Cardiovascular system within normal limits, based on criteria		130
Noncardiovascular defects	24	
Electrocardiographic abnormalities (primary cause of rejection)	12	

DISCUSSION OF RESULTS OF THE EXAMINATION

The chief difficulties encountered in the examinations were concerned with decisions in subjects with murmurs, tachycardia, and borderline hypertension. Many subjects who showed *moderate or marked elevation* of the pulse rate showed *systolic murmurs*, chiefly over the third left intercostal space near the sternum and transmitted along the course of the pulmonary artery. After rest and relaxation, many of these murmurs decreased in intensity or disappeared. In a few subjects with

San Francisco. Table II

Diagnosis	Draft Board and Induction Center Diagnosis: Primary	Draft Board and Induction Center Diagnosis: Secondary	Our Diagnosis: Primary	Our Diagnosis: Secondary	Reject	Accept
Entire group—982					684	274 + 24
Angina pectoris	1	1	1	1	1	
Auricular fibrillation	1	1	2	2	2	
Auricular flutter				1		
Anxiety neurosis	3	2	6		6	
A-V heart block	3		4	5	4	
Buerger's disease	2		2		2	
Bundle branch block			2		2	
Carotid sinus			1		1	
Combination of borderline abnormalities			8		8	
Congenital heart:						
Coarctation			7 + 1 ?		8	
I-V septal	2		25 + 5 ?	1	25	
Patent ductus	1		9		9	
Pulmonary stenosis	1		1		1	
Others	13		16	1	16	
Auricular septal			1		1	
ECG abnormalities	2		12	9	12	
Enlargement by x-ray	11	1	26	1	26	
Enlargement without x-ray	28					
Heart displaced by lung disease			1		1	
Hypertension	278	4	202	10	202	
Funnel chest			2		2	
Hypertension, nervous			31			31
Myocardial disease	19					
Myocardial infarction	1		1		1	
Neurocirculatory asthenia	10		19	11	19	
Nephritis	9		4		4	
Premature beats	2	1	3	4		
Pericarditis	4		3	1	3	
Physiologic murmur			89			89
Poor training			2			2
Rheumatic fever	5		3		3	
Systolic click			3			3
Tachycardia	76	8	17	9	17	
Tachycardia, paroxysmal	5		5	1	5	
Tachycardia, nervous			19	2		19
Syphilitic aortitis	1		2		2	
Vagotonia			1			1
Valvular heart disease:						
Aortic regurgitation	16		71 + 2 ?	6	73	
Aortic stenosis	3		13	27	13	
Aortic insufficiency and mitral stenosis	3		54		54	
Mitral regurg.? etiol.	104		62	1	62	
Mitral regurg., rheumatic	10		26		26	
Mitral stenosis with or without regurgitation	35		63	3	63	
Valvular heart disease	307		6		6	

flat chests these murmurs persisted, and if they remained loud, we were inclined to reject the subject although we are of the opinion that they are of no clinical significance. Cardio-respiratory murmurs were observed frequently and a notation was made on the record of the type, for the benefit of the examiners at the induction centers. Systolic murmurs at the apex, without history of rheumatic fever or scarlet

SAN FRANCISCO. TABLE III

DIAGNOSIS	DRAFT BOARD AND INDUCTION CENTER DIAGNOSIS		OUR DIAGNOSIS		REJECT	ACCEPT
	PRIMARY	SECONDARY	PRIMARY	SECONDARY		
Accepted for cardiovascular status, rejected for:						
Alcoholism			1		1	
Asthma			2 ?		2 ?	
Epilepsy				1		
Homosexuality			1		1	
Hyperthyroidism		6	2	1	2	
Hypopituitarism				1		
Hernia, inguinal			1		1	
Illiteracy				1		
Lymphoma			1 ?		1 ?	
Mental defective			2		2	
Psychoses			4		4	
Psychoneurosis			1		1	
Psychopathic inferior			1		1	
Tuberculosis			5 + 3 ?		5 + 3 ?	

fever, with no evidence of enlargement by physical examination or by x-ray, without electrocardiographic changes, and with no other evidence of cardiac disease, were accepted. Many of these murmurs varied with respiration or posture and were considered of no clinical significance. Mid-systolic murmurs or late systolic clicking sounds at the apex were not considered cause for rejection, in the absence of other evidence of cardiac disease. In a very few instances where such murmurs were very loud in any posture, the subjects were rejected, in view of the probability that, if detected during febrile states or at other examinations, a diagnosis of serious heart disease would be made on the murmur alone.*

Persistent tachycardia and other symptoms and signs generally grouped under the syndrome of neurocirculatory asthenia were frequent causes for rejection by the local boards and at the induction centers. It should be stated that the acceptable limit for the pulse rate had been raised to 110 per minute for our examination, which explains in part the discrepancy on figures for rejection. Between 75 and 100 men have been referred with a diagnosis of neurocirculatory asthenia. It has been obvious in going over this special group that the criteria for making this diagnosis vary widely.

Persistent hypertension was found in our group of subjects in about the same ratio as among all the other groups studied in eastern cities.

X-ray Examination.—The Hodges-Eyster formula for cardiac size appears to be generally acceptable, but in a number of cases a strict

*We were particularly struck with the relatively small number of subjects who had definite evidence of valvular heart disease, including rheumatic heart disease. We have long known that rheumatic fever was relatively uncommon in the Bay region and in other sections of California, but rheumatic heart disease has been known in subjects who had no history of rheumatism. In going over this group of subjects, we made it a point to question a number of them about their residence at the time when they had rheumatic fever, or first had any mention made of valvular heart disease, and found that quite a large number of these young men had their disease begin while they were living in other sections of the country. We are now making a survey of the whole group to find out, if we can, when and where they first had signs or symptoms of valvular heart disease or rheumatic fever or chorea. We may get some interesting data from this study.

application of the rule would exclude some normal subjects. Dr. Earl R. Miller, roentgenologist, has summarized his observations on the roentgenologic examinations and I am incorporating his comments:

"From the radiologist's point of view, it would seem that the best way to examine rejectees from the draft would be by a survey of all of the rejectees by single 14 by 17 posteroanterior films of the chest. This has the advantage of being an objective measure of heart size and shape, to which any of the accepted criteria for heart size could be applied.

"I believe the Hodges-Eyster method of measurement is perhaps as good as any, inasmuch as it is about as objective as it can be, and because it takes into account much more of the patient's build than the cardiothoracic ratio. In addition, the film of the chest demonstrates other conditions, such as lesions in the lung, which would make the person unfit for military service. In questionable cases, fluoroscopy should be added. Fluoroscopy, alone, has the very marked disadvantage of being a subjective record and therefore its validity is open to doubt.

"It is frequently argued that the cost of such an undertaking as mass film surveys of people is very expensive. I think it is quite obvious that the expense of such a survey is very much less than the cost of the care of patients missed by failing to make such a survey.

"In addition, this record would be of inestimable value to the patients themselves for comparison in future years when other diseases make their appearance.

"It would seem to me that a little leeway should be allowed in rejecting patients for heart size when their heart is apparently slightly above normal in size and all other things appear to be within normal limits. It would seem that a strict application of some rules about size does not always allow a correct interpretation of the cardiac status."

Electrocardiography.—We had a number of electrocardiograms of individuals who seemed to be entirely normal and whose cardiac sounds were either normal or showed so-called functional murmurs where the electrocardiogram showed prolongation of the P-R interval to a 0.22 second or more, and in some instances to 0.24 second in one or two leads. We had some difficulty in evaluating this finding and we are keeping these records together for special study in the near future. We hope to be able to follow these subjects for some time.

Several of the chief examiners have submitted a number of observations which are incorporated as follows:

1. *Dr. Edwin L. Bruck.*—"I think the regulations for examination of selectees should be made most carefully by cardiologists, and that all doubtful murmurs should be submitted to unusual scrutiny, for I am sure that many of the murmurs which have rejected young men from the Armed Forces are not important in so far as cardiac pathology is concerned. Further clarification in the regulations, as well as in the minds of many examiners for the Army and Navy, is going to be necessary before proper acceptance or deferment of individuals with heart murmurs can be made. Not only the so-called functional murmurs but

also questionable murmurs should be examined with the utmost scrutiny, and other examinations of the heart should be carried out in greater detail, because we are sure that many of these murmurs may come from mild congenital defects or unimportant large vessel changes and have no significance when the heart is normal from the standpoint of x-ray, electrocardiography, vital capacity, exercise tests, pressure, pulse rate, etc.

"The determination of the size of the heart by ordinary clinical methods of percussion and palpation, as against the x-ray examination, is always a surprise to me. That is, I am surprised that the two methods of examination coincide so often. There is no substitute, of course, for proper x-ray examination, but the evaluation of heart size from x-ray examination is sometimes difficult. According to formula, we saw many hearts which were large by that method and within the normal range of size by all other methods. Many times these were on the basis of formula or the nomogram in which the height and weight of the individual were abnormal in proportion. That is, very tall, thin people were apt to be construed as having hearts that were enlarged when, by all other methods, they were within the normal range.

"As to the matter of rapid pulses with normal sinus rhythm, the nervous influence must be a very large one in this group of men, engendered by either one of two fears. The fear of being taken into the Army when they do not want to go or the fear of being left out when they do want to go. I do not believe that these conditions can be classified as cardiac neurosis or neurocirculatory asthenia without a number of other findings which were lacking in most instances. This group deserves further examination and further study."

2. *Dr. J. Marion Read.*—"We found a great many patients who actually had normal blood pressures and who had been 'tagged' as hypertensives. Of course, the same was true to a certain extent in many of the subjects with murmurs, but I was particularly struck by the former. It is difficult to explain this situation. Probably many of the subjects were 'pepped up' and a little hypertonic at the time of their first examination, but were not really hypertensives."

3. *Dr. J. K. Lewis.*—"With reference to heart size by x-ray, I feel that the present allowable limits might be increased with safety. I would suggest a further study of the rejected group, particularly the borderline cases and those in whom an exact diagnosis could not be made."

4. *Dr. David A. Rytand* (Dr. Rytand substituted for Dr. J. K. Lewis).—"I was impressed, as might have been expected, by gross inequalities in the general level of practicing physicians; heart disease diagnosed when not present, on the one hand, as against the number of patients with coarctation who knew what was wrong with them. I am not yet convinced that men should be rejected because their arterial pressures are a few millimeters over certain arbitrary standards. Likewise, I feel we pay too much attention to lone systolic murmurs (except at the base) and to their transmission."

5. *Dr. F. L. Chamberlain.*—"In the draftee examination research, I doubted the accuracy of the x-ray heart measurements according to the Eyster formula. It would be very helpful if the patients rejected because of heart size could be followed over a period of years.

"I felt that there was considerable difference of opinion among members of our Board with respect to the interpretation of murmurs. Accordingly, if a future study is done, I believe standards should be

agreed on in an early 'skull session' in which criteria could be agreed upon.

"I commend the study especially for its educational value to members of the Board as well as to visiting house officers."

RECOMMENDATIONS

It is my opinion that in this region of the country the number of reclaimed men of draft age was great enough to make the undertaking worth while. The relatively low incidence of valvular heart disease is in striking contrast with the experience in the other four cities where similar examinations were conducted.

If a sufficient number of qualified cardiovascular examiners were available, similar surveys could be made in all the larger centers of population in the country. However, it is my opinion that enough qualified examiners could not be recruited at this time to make these examinations. Alternative plans would be (1) to strengthen the staffs at the induction centers by the inclusion of highly qualified specialists in this field and other fields, or (2) to use the services of cardiovascular specialists wherever possible as consultants for the induction centers. There is apparently a reservoir of men who have been placed in the 4F category by the examiners at the local board with or without the advice of Medical Advisory Boards, and, unless they are re-examined by competent physicians, these men will remain in the 4F category indefinitely.

It is the hope of our special examiners that we may be able to follow some of the groups of subjects who had conditions of unusual interest. We would like to know more about the subsequent course in patients with hypertension and tachycardia. We are interested in the psychological aspects of both of these problems. In subjects who have borderline conditions and are accepted for full military service, it would be desirable to have the serial numbers of these men so that we may be able to follow their course in the years to come. The serial numbers could be affixed to our records and follow-up studies could be made through the special examiners who have participated in this study. A number of our subjects who had borderline tachycardia or hypertension have been accepted for service, which increased our percentage of those placed in the category of 1A, whereas in other studies a number of these were probably excluded from service. I am of the opinion that those with slight hypertension probably will make better soldiers under trying and difficult conditions than the average, whereas those who had effort syndrome or neurocirculatory asthenia probably would develop the picture of so-called shell shock at the first opportunity.

All those physicians who participated in our examinations on a voluntary basis did so gladly and with a fine spirit of cooperation. Those who received compensation for their services likewise devoted themselves wholeheartedly to their tasks after long and arduous days at the hospital.

A DETAILED ANALYSIS OF THE ELECTROCARDIOGRAMS OF 500 R.C.A.F. AIRCREW

SQUADRON LEADER C. B. STEWART AND
FLIGHT LIEUTENANT G. W. MANNING

IN A previous report[5] a gross analysis was made of the wave complexes and time relationships of the electrocardiograms of 2,000 Royal Canadian Air Force aircrew between the ages of 18 and 32 years. The present report contains a more detailed analysis of an additional 500 electrocardiograms showing the variation in form, amplitude, and time relationships of the wave complexes.

The characteristics of the normal electrocardiogram are described in most textbooks or physiologic treatises on cardiology, but the authors differ somewhat in their definitions of the degree of variation to be expected in healthy individuals. Almost all of them set definite limits for the so-called "normal range" of amplitude or duration of each complex or interval. Occasionally, these standards are based on the study of a small number of electrocardiograms, or are admitted to be arbitrary, but more frequently the number of individual records is not stated. An exact determination of the range of amplitude or duration of certain complexes is largely of academic interest, but the establishment of significant standards for the complexes or intervals which are of chief diagnostic aid is of considerable practical importance.

In textbooks published within the last ten years, the limits of the normal P-R interval are variously defined as 0.12 to 0.18 second by Lewis;[6] 0.13 to 0.16 second with 0.21 second as the extreme limit of normal by Wright;[14] 0.12 to 0.20 second by White,[12] by Graybiel and White,[4] and by Maher and Wosika;[7] less than 0.20 second by Master[9] and by Carter,[2] and with upper limits varying from 0.16 to 0.21 second depending upon body size and the heart rate by Ashman and Hull.[1]

The normal limits of R wave amplitude in the lead showing the greatest deflection are described as 4 to 16.5 mm. in 52 normal adults, by Lewis;[6] 5 to 35 mm. by White,[12] and by Graybiel and White;[4] 4 to 22 mm. by Ashman and Hull;[1] 7 to 15 mm. by Master,[9] and 5 to 20 mm. arbitrarily accepted as the normal range by the Criteria Committee of the New York Heart Association[3] and by Maher and Wosika.[7]

Lewis[6] states that the P wave is always positive in normal young adults in all leads, but Ashman and Hull[1] report that a negative P wave occurs normally on rare occasions in Leads I and II, and that a negative or diphasic P_3 occurs in 4 to 5 per cent of normal records. White[12] states that inversion of the P wave is abnormal in Lead I, except in

congenital dextrocardia, and always in Lead II. Carter[2] also defines a negative P_2 as a definite abnormality.

White,[12] in 1931, stated that T_1 and T_2 are always upright in normal electrocardiograms unless the record is taken during forced respiration, but later, in 1941, he found, with Chamberlain and Graybiel,[13] that inversion of the T waves in Lead II may occur normally as the result of positional and sympathetic nerve effects. Ashman and Hull[1] report a few cases in which T_2 was inverted in the absence of heart disease.

Similar and even more marked discrepancies occur in the definitions of deviation of the electrical axis of the heart. White[12] defines the normal axis deviation as 0 to 90 degrees when plotted on the Einthoven triangle. The Criteria Committee of the New York Heart Association[3] set 30 to 90 degrees as the normal range when their standards are expressed in the same scale, while Ashman and Hull[1] define the limits of normality as 40 to 90 degrees.

When a limited group on either side of the average is labeled the "normal range" for the amplitude or time interval of any electrocardiographic complex, the inference is that measurements outside that range are abnormal, although in practice they sometimes do not indicate any definite cardiac abnormality. Different methods have been used by different cardiologists in setting the limits which they describe as the normal range. Few writers define the system which they follow, but it is obvious that two are used. By some, the normal zone is so widely defined as to include some borderline abnormals as well; by others the zone of greatest distribution is accepted as the normal, excluding the more extreme and less frequent normal variations. With the wide range, one would correctly label as abnormal any measurements beyond the established limits, provided the standards had been based on a true random sample of the normal population, and adequate provision had been made for chance variation beyond those observed limits. In many reports, however, no statistical tests have been applied to determine the chance variation beyond the limits recorded in that particular series of observations. With the narrower definition, certain borderline normal electrocardiograms will be incorrectly placed in the abnormal class. Obviously, the narrower the limits are made, the more cases will be wrongly excluded from the normal group.

In some instances, limits of normality are defined but at the same time completely disregarded. For example, it seems paradoxical to state, as one writer does, that the upper limit of normality of the P wave is 1, 2.5, and 2 mm., in the three standard leads respectively, and to follow this with a statement that the increase in height beyond these limits is not an adequate basis for a diagnosis of abnormality.

It would probably be preferable to eliminate the use of the terms "normal" and "abnormal" and to accept such terms as "of no significance," "of slight significance," or "of definite significance," de-

pending upon the degree of deviation from the average picture. In practice, the cardiologist assesses the clinical importance of any electrocardiographic peculiarity on this basis, considering both the degree of aberration from the so-called normal range and the presence or absence of associated clinical, radiological, or other electrocardiographic abnormalities. In the absence of other findings, an electrocardiographic measurement slightly beyond what is usually accepted as the normal range is considered of slight significance, such as a P-R interval of 0.22 second. However, a P-R interval of 0.40 second, which is definitely beyond this range, may alone be considered of diagnostic significance.

There is undoubtedly an overlapping of the normal and abnormal in the electrocardiogram as in most measurements relating to human physiology, and the setting of exact limits of normality is impossible. After an attack of rheumatic fever an individual may have had an increase in the P-R time from 0.14 to 0.20 second due to an organic interference with the conduction mechanism, while a normal individual occasionally may have a P-R interval of 0.22 second with no history of cardiac illness, no clinical abnormalities, and no sequelae to suggest heart disease. Rather than accepting one rigid standard in preference to another, it seems desirable, therefore, to set the extreme limits of normal beyond which no normal electrocardiogram would be expected to occur and to provide some index of the possibility of normals or abnormals occurring at various levels below these limits.

In this report, data are presented to show the variation to be expected in the electrocardiograms of a comparatively large group of healthy young male adults. By use of the standard deviation of the mean, in numerical data conforming to the normal curve of distribution, the limits can be determined at which deviations from the average become slightly or definitely significant. If three times the standard deviation is added to, or subtracted from, the average measurement, the upper and lower limits of the distribution are obtained with an error of approximately 0.3 per cent. In other words, there would be only about three chances in a thousand of finding a measurement greater than the upper limit or less than the lower limit in the electrocardiogram of a healthy man of this age group. One would be well justified, then, in calling abnormal any measurement which fell beyond three times the standard deviation. By adding or subtracting twice the standard deviation, one obtains the limits which may be accepted as those of practical significance. Less than 5 per cent of normal electrocardiographic measurements will fall above or below these limits. If a measurement falls between two and three times the standard deviation, one would have to be particularly careful to seek corroborative clinical or other data before considering the electrocardiographic finding significant. This method gives information as to the full limits of the normal range, and the limits in which corroborative evidence is

necessary to determine significance. It also permits an estimate of the chance of error in calling a borderline electrocardiogram normal or abnormal. Calculation of the standard error of the mean gives an indication of the degree of error in accepting the mean of this series of five hundred as indicative of the mean of an unlimited group of normal young men.

MATERIAL AND METHODS

The present series of electrocardiograms were taken on 500 R.C.A.F. aircrew trainees between the ages of 18 and 32 years, the majority being between the ages of 18 and 26 years. All had passed the standard R.C.A.F. medical examination for "Fitness for Flying" at a recruiting center, and had had a complete medical recheck at the time that the electrocardiograms were recorded. In addition, those who showed questionable or definite electrocardiographic abnormalities were again rechecked clinically and, in many cases, by further electrocardiographic records. Although x-ray plates had been taken on all individuals on enlistment, additional plates were taken in many cases to recheck cardiac measurements.

A portable Cambridge (English) electrocardiograph was used, making a record on a single film of five seconds' duration for each of the three leads. The subject rested for approximately five minutes in the recumbent position before the recording was made. The three standard leads were used, the deflection of the galvanometer string being standardized before each lead (1 cm. – 1 mv.). Measurements of the amplitude of waves were made to the nearest 0.2 mm. from the top of the base line in positive waves and from the bottom in negative waves. Time intervals were measured to the nearest 0.02 second along the bottom of the base line for positive waves and the top of the base line for negative waves. The repetition of those records which showed various abnormalities provided a check on the recording technique and showed that the records were duplicated with a high degree of accuracy in all significant details.

There had been no change in the medical standards employed in the selection of this group and of the 2,000 whose electrocardiograms were previously reported, nor in the age grouping of the men.

A comparison of the data obtained in the analysis of the electrocardiograms of the present series and the previous group of 2,000 is shown in Table I.

There are no statistically significant differences between the two groups in the above measurements nor in other measurements made according to the same standards of accuracy in both series. It may be concluded from the close similarity of the data in the two groups, that the series of 500 is as representative a sample of the aircrew population as the larger one of 2,000 men.

TABLE I

COMPARISON OF PRESENT 500 ELECTROCARDIOGRAMS WITH 2,000 PREVIOUSLY REPORTED[5]

		SERIES OF 2000 ECG		SERIES OF 500 ECG	
		NO.	PER CENT	NO.	PER CENT
Category 1		27	1.35	9	1.8
Category 2		358	17.90	66	13.2
Category 3		1307	65.35	331	66.2
Category 4		299	14.95	92	18.4
Category 5		9	0.45	2	0.4
		2000	100.00	500	100.0
Positive P wave	(Lead I)	1973	98.60	497	99.4
	(Lead II)	1962	98.10	497	99.4
	(Lead III)	1581	79.00	401	80.2
P-R interval between 0.12-0.20 second	(Lead II)	1949	97.45	484	96.8
R wave over 5 mm.	(Lead I)	1236	61.80	311	62.2
	(Lead II)	1964	98.20	492	98.4
	(Lead III)	1468	73.40	371	74.2
Positive T wave	(Lead I)	1997	99.85	500	100.0
	(Lead II)	1989	99.45	499	99.8
	(Lead III)	1425	71.25	356	71.2

TABLE II

DIRECTION AND AMPLITUDE OF P WAVE

DIRECTION					AMPLITUDE IN MM.				
LEAD	POS.	NEG.	DIPHASIC	ABSENT	MEAN AMP.	STANDARD DEVIATION OF MEAN	STANDARD ERROR OF MEAN	SIGNIF. LIMITS (± 2 S.D.)	HIGHLY SIGNIF. (± 3 S.D.)
I	497	0	0	3	0.7	0.28	0.01	0.1 to 1.3	-0.1 to +1.5
II	497	0	1	2	1.4	0.53	0.02	0.3 to 2.5	-0.2 to 3.0
III	401	48	41	10	0.7	0.59	0.03	-0.5 to +1.9	-1.1 to +2.5

ANALYSIS OF DATA

P Waves.—Table II shows the direction and amplitude of the P waves in 500 electrocardiograms.

None of the records showed consistently negative P waves in Leads I and II, but occasional negative complexes appeared in a few records as a result of auricular extrasystoles. Only one record showed diphasic P waves in Lead II. The P wave was negative in Lead III in forty-eight records (9.6 per cent) and diphasic in forty-one others (8.2 per cent).

The amplitude of the P waves of the 500 records followed the normal curve of distribution with less than 5 per cent of the total falling outside limits set by twice the standard deviation (2.4 per cent in Lead I, 4.2 per cent in Lead II, and 3.8 per cent in Lead III). Only four records showed a maximum P wave in excess of 2.5 mm. in Lead II, and none had P waves of less than 0.5 mm. in all three leads. Slight varia-

tions were frequently noted in the amplitude of the P wave throughout a lead, and in twelve records this variation amounted to 0.5 to 1.5 mm. difference between the maximum and minimum complexes. In two records P_3 changed from a low positive wave to diphasic to negative and back to positive. The variations in amplitude were probably associated with the respiratory cycle.

Table III shows the average duration of the P wave in the three leads.

TABLE III

DURATION OF P WAVE

LEAD	MEAN P TIME	STANDARD DEVIATION OF MEAN	STANDARD ERROR OF MEAN	SIGNIF. LIMITS (± 2 S.D.)	HIGHLY SIGNIF. LIMITS (± 3 S.D.)
I	0.08	0.018	0.0008	0.04 to 0.12	0.03 to 0.13
II	0.09	0.015	0.0007	0.06 to 0.12	0.05 to 0.14
III	0.08	0.018	0.0007	0.04 to 0.12	0.03 to 0.13

Broad P waves, defined by the Criteria Committee of the New York Heart Association as those of more than 0.10 second, were present in twenty records in Lead I, in thirty-seven records in Lead II and in twelve records in Lead III. Only one of these records showed broad P waves in all three leads and ten others in two leads. The point at which P wave duration is significantly prolonged would seem from this series to be 0.12 second.

Although P waves of very low amplitude also tended to be of short duration, there was only a low positive correlation of 0.31 in the whole group between wave amplitude and duration. Waves of high amplitude might be either of relatively short duration or slow and broad.

Table IV shows the number of records which had a rounded, pointed, or notched P-wave summit.

TABLE IV

SHAPE OF P WAVE

LEAD	P ROUND	P POINTED	P NOTCHED	OCC. POINTED WAVE
I	466	15	17	—
II	417	49	27	5
III	419	38	19	4

The majority of the P waves formed a rounded summit, but a considerable number of records showed a sharp or pointed P wave, and over 5 per cent were notched in varying degree at the apex. Five records in Lead II and four in Lead III showed varying sharp and rounded P-wave complexes. The notching was not correlated with extremes of P-wave amplitude or duration, nor with any other electrocardiographic peculiarity, and it did not usually occur in all leads of a record.

P-R Interval.—The P-R interval was measured in all three leads from the beginning of the P wave to the beginning of the QRS com-

plex, whether positive or negative. The average duration was calculated from these measurements, but, if the interval was borderline or prolonged in any lead, allowance was made for an absent or isoelectric Q wave as recommended by Graybiel and White.[4]

Table V shows the average duration of the P-R interval in each lead, the standard deviation from the mean, and the calculated limits of the distribution.

TABLE V

P-R INTERVAL

LEAD	MEAN P-R DURATION	STANDARD DEVIATION OF MEAN	STANDARD ERROR OF MEAN	SIGNIF. LIMITS (± 2 S.D.)	HIGHLY SIGNIF. LIMITS (±3 S.D.)
I	0.15	0.026	0.001	0.10 to 0.20	0.07 to 0.23
II	0.16	0.025	0.001	0.11 to 0.21	0.09 to 0.24
III	0.15	0.027	0.001	0.10 to 0.20	0.07 to 0.23

The incidence of P-R intervals of different durations formed a normal curve of distribution on either side of the mean. The average duration and limits of the P-R distribution were slightly greater in Lead II than in the other leads, the limits as set by twice the standard deviation being 0.11 second to 0.21 second. However, 1.4 per cent of this group of healthy young men had electrocardiograms with a P-R interval of more than 0.20 second in Lead I, 2.2 per cent with P-R greater than 0.21 second in Lead II, and 1.8 per cent with P-R greater than 0.20 second in Lead III. Of these, 0.6 per cent had a P-R in excess of 0.24 second, the upper limits of normal set by three times the standard deviation of the mean.

It cannot be stated with absolute certainty that these individuals with apparently prolonged P-R intervals were normal, but careful clinical history and examination and radiological study revealed no evidence of cardiac disease. It would appear from the above statistical data that approximately this number of normal young men might be expected to have P-R intervals greater than 0.20 second. However, this does not prove that these men will not later develop definite evidence of cardiac disease associated with poor conduction of the cardiac impulse. At present, however, they are apparently normal, athletic young men with good cardiac function, and the electrocardiographic evidence of prolonged P-R interval seems not to be significant.

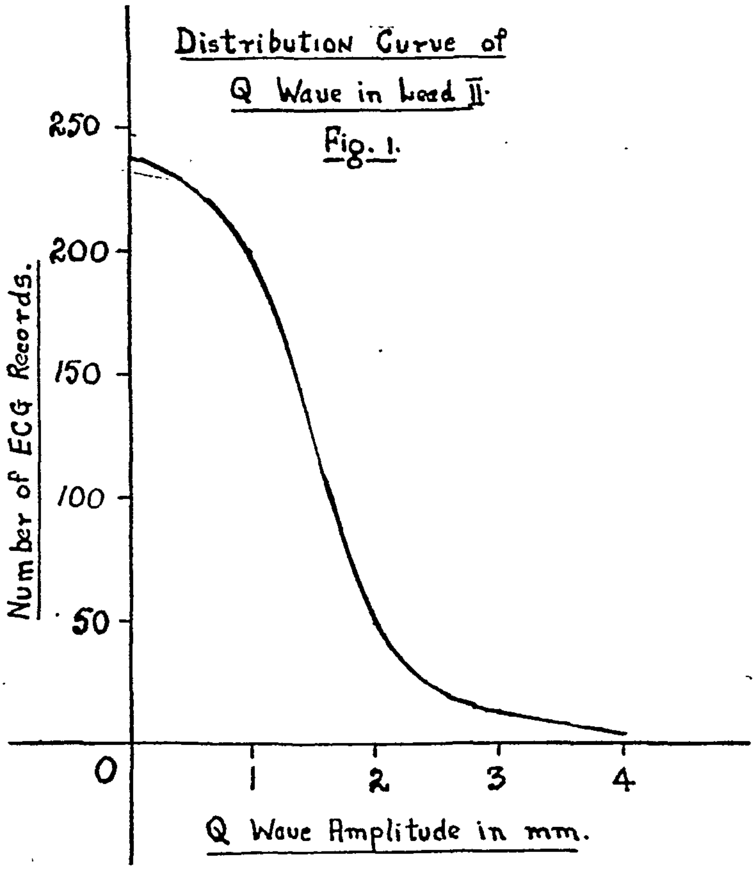
The four men whose electrocardiographic records showed P-R intervals of more than 0.24 second were also apparently normal young men with no abnormality except the long P-R conduction time of 0.26, 0.26, 0.32, and 0.36 second, respectively. The electrocardiographic records of these men are discussed more fully in another paper.[5] If these extreme P-R measurements are excluded from the series, the calculated mean and the standard deviation are not reduced to any significant degree.

Slight depression of the P-R segment below the isoelectric line was common but it exceeded 0.5 mm. in only nine records. It occurred in all three leads in six cases and in only Lead II in three others, and probably represented the auricular T wave.

TABLE VI

Q-WAVE AMPLITUDE

LEAD	Q PRESENT	Q ABSENT	MEAN AMP.	OBSERVED RANGE (IN MM.)
I	143	357	0.9	0 to 4
II	290	210	1.1	0 to 4
III	305	195	1.4	0 to 6



Q Wave.—Table VI shows the incidence of Q waves and their average amplitude in the series of 500 electrocardiograms.

The distribution of the Q-wave amplitude was not according to the normal curve, and limits set by the standard deviation would be misleading. The observed extremes are noted in each lead. Fig. 1 shows the curve of distribution of the Q-wave amplitude in Lead II, the other leads being similar.

Measurements of the Q wave alone are of little value unless compared with the maximum R-wave deflection of the same record. A Q wave is considered abnormally deep according to the standards of the Criteria Committee of the New York Heart Association[3] if Q_1 is greater than 15 per cent of the largest QRS deflection in any lead, Q_2 greater

than 20 per cent, and Q_3 greater than 25 per cent. These criteria do not hold in electrocardiograms showing a high voltage of the QRS group or for Leads II and III if there is right axis deviation. In defining a deep Q_3, Pardee[10] also excluded records which had an S wave in the QRS_3 complex.

The distribution of the percentage relationship of the Q waves present in Lead II to the maximum R is shown in Fig. 2. In the other leads the distribution was almost identical.

The majority of the records had a Q-wave amplitude which was less than 10 per cent of the maximum R, but a small number exceeded 20 per cent. Table VII presents data on the Q waves which showed a high percentage relationship to the maximum R.

TABLE VII

DEEP Q WAVES

RECORD NO.	MAXIMUM R WAVE	Q WAVE AMPLITUDE			PERCENTAGE RELATION OF Q WAVE TO MAXIMUM R	NORMAL LIMITS	AXIS DEVIATION (DEGREES)	S WAVE (AMP.)
		LEAD I	LEAD II	LEAD III				
1	R_1 9	2			22.2	15	66	2.5
2	R_1 11	2			18.2	15	19	3
3	R_1 12	3			25.0	15	3	2
4	R_2 13	4			30.8	15	40	0
5	R_1 12	2			16.6	15	10	0
6	R_1 8.5	1.5			17.7	15	30	1
7	R_2 18.0		4		22.2	20	95 RAD	0
				6	33.3	25	95 RAD	0
8	R_2 19		4		21.0	20	95 RAD	4.5
				5	26.3	25	95 RAD	1
9	R_3 11.5			3	26.1	25	87	0
10	R_2 9.5			3.5	36.8	25	65	0
11	R_2 12			3.5	29.2	25	87	0
12	R_2 7			2	28.6	25	38	2
13	R_1 5			1.5	30.0	25	15	3
14	R_3 7			2	28.6	25	97 RAD	0
15	R_2 17			4.5	26.5	25	93 RAD	0
16	R_1 8.5			3	35.3	25	59	0

This table shows that six records had Q_1 waves which were more than 15 per cent of the maximum R. Two Q_2 waves were more than 20 per cent of the maximum R. In Lead III ten records showed a Q wave which was more than 25 per cent of the greatest R amplitude. Two of these records had deep Q waves both in Leads II and III. None showed deep Q waves for all leads. None of the electrocardiograms had high voltage QRS, but four records showed a right axis deviation and were therefore excluded from the deep Q wave group by definition. Two others had borderline axis deviation of 87 degrees, but were included as deep Q waves. Two records which had S waves in Lead III would also be excluded according to Pardee's standards. Only twelve records, therefore, showed deep Q waves and had an axis deviation within the normal range. In these cases there were no other significant electrocardiographic abnormalities and the men were clinically normal in all respects.

R Waves.—The positive deflection of the QRS complex was considered as the R wave whether larger or smaller than the negative deflections. In a few records with more than one positive deflection, the maximum wave was included in this series as the R wave.

Table VIII shows the average amplitude, standard deviation, and range of the R wave.

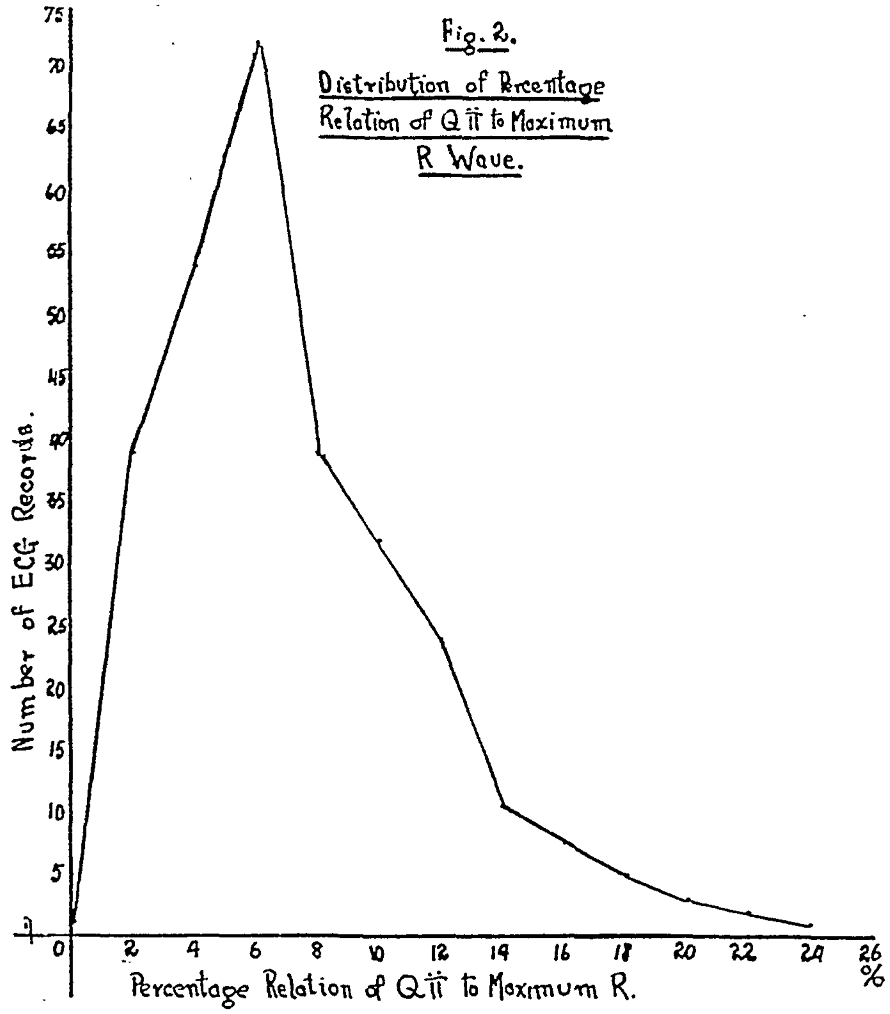


TABLE VIII

R-WAVE AMPLITUDE

LEAD	MEAN AMPLITUDE	STANDARD DEVIATION OF MEAN	STANDARD ERROR OF MEAN	SIGNIF. LIMITS (± 2 S.D.)	PER CENT ABOVE OR BELOW 2 S.D.
I	6.6	2.7	0.12	1.2 to 12.0	3.8
II	14.1	4.0	0.18	6.1 to 22.0	5.0
III	9.3	4.7	0.21	0.0 to 18.7	1.2

Two records had no positive wave in the QRS complex in Lead III. In the other leads R was present in all records. An R wave of less than 5 mm. amplitude occurred in 131 records in Lead I, in 7 records in Lead II, and in 103 records in Lead III. A number of these occurred in conjunction with right or left axis deviation, but there were a large number of records with normal axis deviation which showed low volt-

age of the R wave in Leads I and III. Only one record had R waves of less than 5 mm. in all three leads. On the other hand, 27 records in Lead II and one in Lead III showed an R wave in excess of 20 mm., the arbitrarily accepted standard of normality. The curves of distribution of the R-wave amplitude in Leads I and III are slightly skew, but in Lead II the distribution is normal. It is suggested from this curve that the upper range of significance might be set at 22 mm., and the lower at 6 mm. (S.E. ± 0.18) with extreme limits of normal of 2 to 26 mm.

In fourteen records there were two positive waves in the QRS complex of Lead III. This usually consisted of a small upright deflection of 1 to 2 mm. followed by a negative wave varying in amplitude from 1 to 8 mm. A second positive wave of 3 to 10 mm. amplitude was sometimes followed by a second negative wave of 1 to 3 mm. In most cases the first positive wave was very small and was followed by an apparently normal QRS complex. In a few records a small sharp upstroke of 0.5 to 1 mm. followed the S wave of what appeared to be a normal QRS complex. In some electrocardiograms a notching of the upstroke of the R wave near the base gave the appearance of an additional positive and negative wave preceding R, but the notch did not extend below the isoelectric line. In three records with additional positive waves there was an associated right axis deviation, the QRS consisting of a positive wave of 1 mm., a negative wave of 7 to 8 mm., and a second positive wave of 1 mm. This looked like an inverted QRS, but the P and T waves were positive.

A number of records showed slight variations in QRS amplitude throughout a lead, and two showed a marked change with the respiratory cycle from a low notched QRS_3 of 2.5 mm., to an unsplintered wave of 6 mm. amplitude.

S Wave.—The number of records showing S waves and the average amplitude are shown in Table IX.

TABLE IX

S-WAVE AMPLITUDE

LEAD	S PRESENT	S ABSENT	MEAN AMPLITUDE
I	432	68	2.8
II	382	118	2.5
III	265	235	2.3

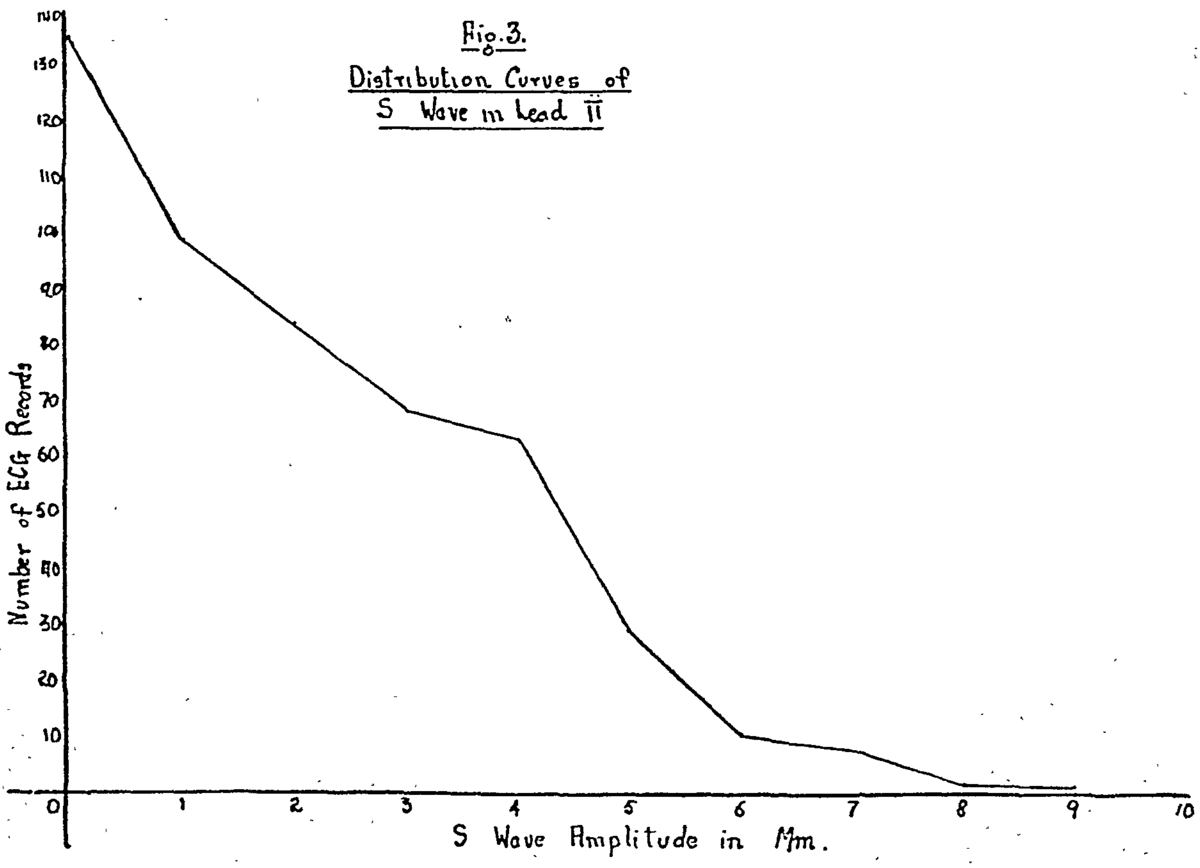
S waves were present in about three-fourths of the records with a mean amplitude of approximately 2.5 mm. Fig. 3 shows the curve of distribution of the S-wave amplitudes in Lead II. Since it is not a normal curve of distribution, the limits defined by the standard deviation from the mean are not calculated. Maximum S waves of 9 to 10 mm. occurred in three records, but the majority were 1 to 3 mm. in amplitude.

Slurred, Splintered, or Notched QRS.—The QRS complex showed varying degrees of slurring, splintering, or notching in 13, 4, and 130 records, in Leads I, II, and III, respectively. Two of the records showed slurring or splintering in all three leads and one in Leads II and III. This irregularity occurred nearer the apex of the QRS in some leads than in others in the same record, and would be considered an abnormal feature by some standards.[3] There was no consistent relation between slurring or splintering and other electrocardiographic abnormalities, although some of these records had a QRS interval which reached the maximum limits of normal. The individuals were all apparently normal clinically.

TABLE X

QRS INTERVAL

LEAD	MEAN DURATION	STANDARD DEVIATION	STANDARD ERROR	SIGNIFICANT LIMITS (± 2 S.D.)	HIGHLY SIGNIFICANT LIMITS (± 3 S.D.)
I	0.07	0.016	0.0007	0.04 to 0.10	0.02 to 0.12
II	0.07	0.016	0.0008	0.04 to 0.10	0.02 to 0.12
III	0.07	0.017	0.0007	0.04 to 0.10	0.02 to 0.12



QRS Interval.—The duration of the QRS interval is shown in Table X. The upper limit of QRS time, in this series, as set by twice the standard deviation, corresponds with the usually accepted limit of 0.10 second. None of the records had a QRS time above this limit in Lead I, but five exceeded 0.10 second in Lead II, and six in Lead III. There was no

clinical abnormality associated with the finding of an increased QRS in these cases and this number might be expected to occur among normal young men. A QRS of more than 0.12 second might, however, be considered definitely abnormal.

T Wave.—The direction and amplitude of the T wave are shown in Table XI.

TABLE XI

DIRECTION OF AMPLITUDE OF T WAVE

	DIRECTION				AMPLITUDE					
LEAD	POSITIVE	NEGATIVE	DIPHASIC	ABSENT	MEAN AMP.	STANDARD DEVIATION OF MEAN	STANDARD ERROR OF MEAN	SIGNIF. LIMITS (± 2 S.D.)	PER CENT BEYOND SIGNIF. LIMITS	HIGHLY SIGNIF. LIMITS (± 3 S.D.)
I	500	0	0	0	3.0	1.0	0.04	1.0 to 5.0	3.4	0 to 6.0
II	499	0	1	0	3.8	1.4	0.06	1 to 6.6	3.8	-0.4 to 8.0
III	356	74	66	4	0.8	1.3	0.06	-1.4 to 3.4	4.2	-3.1 to 4.7

Twenty-eight per cent of the records showed diphasic or negative T waves in Lead III, but only one record had diphasic T waves in Lead II. The curve of distribution was a normal one with less than 5 per cent falling outside the limits set by twice the standard deviation.

U Wave.—U waves were present in 250 records in Lead I, in 274 records in Lead II, and in only 61 records in Lead III. Almost all of the U waves were of a very low amplitude, the average being approximately 0.2 mm.

RT-ST Segment.—The level of the RT or ST segment was measured to the nearest 0.2 mm. with relation to the post-T isoelectric line. In the majority of the records there was no measurable elevation or depression of the RT or ST segment. However, 77 records had a slight RT or ST elevation of 0.6 mm. in Lead I, and two other records showed a depression of 0.5 mm. Only one record had an RT elevation of more than 1 mm. in Lead I. Fifty-nine records in Lead II had an elevation of the RT-ST segment averaging 0.75 mm. Five of these showed an elevation in excess of 1 mm. (1.5 to 2 mm.). Thirty-four other records showed slight depression of the RT-ST segment of 0.8 mm., none of these exceeding 1 mm. In Lead III twenty-four records showed an elevation of the RT-ST segment averaging 0.6 mm. but none exceeded 1 mm. Seventy-nine other records showed a slight depression of the interval of 0.76 mm. and three of these were 1.5 mm. below the isoelectric line.

None of these records which showed a depression or elevation of the RT-ST segment exhibited any other significant electrocardiographic abnormality, and the men were clinically normal. Slight elevation or depression of the RT-ST segment of less than 1 mm. is not usually considered significant. It is possible that the above cases which showed an elevation or depression somewhat more than the accepted standards are

also of little significance, when not associated with T-wave changes or other peculiarities in the electrocardiographic complexes.

There was considerable variation in the level at which the R or S wave began to thicken and slope into the ST segment. In Lead I three records showed a slightly high take-off of 2 to 2.5 mm. and two showed a low take-off of 1.5 to 2 mm. below the isoelectric line. In Lead II twenty-five records showed a thickening and sloping into the RT segment 1.5 to 4 mm. above the base line, and four other records sloped into the ST segment 1.5 to 2 mm. below the isoelectric line. In Lead III sixty-three records had a high take-off of 1.5 to 7.5 mm. and six with a low take-off of 2 to 4 mm. The thickening and sloping of the R or S wave was not associated with a significantly elevated or depressed RT-ST segment although minor degrees of elevation or depression were frequently associated with the high or low take-off.

In most records the upstroke of the R wave was quick and sharp but in eight records with no Q wave the R wave was thickened and sloping from the PR interval for a height of 1 to 2 mm., and in one case, 6 mm.

Q-T Time.—The Q-T time was measured from the beginning of the QRS complex to the end of the T wave. Table XII shows the average duration in 500 records without reference to heart rate.

TABLE XII

Q-T TIME

LEAD	MEAN Q-T TIME	STANDARD DEVIATION OF MEAN	STANDARD ERROR OF MEAN	SIGNIF. LIMITS	HIGHLY SIGNIF. LIMITS
I	0.33	0.03	0.001	0.27 to 0.39	0.24 to 0.42
II	0.34	0.03	0.001	0.28 to 0.40	0.25 to 0.43
III	0.33	0.03	0.001	0.27 to 0.39	0.24 to 0.42

The above figures give some indication of the range of Q-T time but consideration must also be given to the relation of this interval to the heart rate. The Criteria Committee of the New York Heart Association[3] state that a correction for rate can be made by the formula Q-T = K $\sqrt{\text{cycle length}}$ and that the Q-T interval is regarded as prolonged if K exceeds 0.392 in men. Table XIII shows the mean K values and range of distribution in this group of 500.

TABLE XIII

CORRECTED Q-T TIME (K VALUE)

LEAD	MEAN K VALUE	STANDARD DEVIATION OF MEAN	STANDARD ERROR OF MEAN	SIGNIF. LIMITS (± 2 S.D.)	HIGHLY SIGNIF. (± 3 S.D.)
I	0.38	0.03	0.001	0.32 to 0.44	0.29 to 0.47
II	0.38	0.03	0.001	0.32 to 0.44	0.29 to 0.47
III	0.38	0.03	0.001	0.32 to 0.44	0.29 to 0.47

This table shows that the upper limits of the range of the corrected Q-T values are considerably higher than 0.392 in this group of young

men. In Lead I, 142 records, in Lead II, 197 records, and in Lead III, 158 records had a corrected Q-T time of 0.40 second or greater, while approximately 2 per cent of the records had a corrected Q-T time in excess of 0.44 second.

Axis Deviation.—Separate calculations were made of the axis deviation of each electrocardiogram on mimeographed duplicates of the Einthoven triangle illustrated by White.[12] Mathematical calculations on a large number of records showed that the margin of error by this method was less than 5 degrees.

Table XIV classifies the records according to the degree of axis deviation.

TABLE XIV

AXIS DEVIATION

RANGE OF AXIS DEVIATION (DEGREES)	NUMBER OF RECORDS
Less than 0	22
0 to 30	22
31 to 90	414
Over 90	42

By certain standards, only 22 records would be considered as left axis deviation, and, by others, 44 records. Forty-two showed right axis deviation. The mean axis deviation of the whole group was 65 degrees with a standard deviation of ±29 degrees and a standard error of ±1.3 degrees. The measurements of axis deviation were distributed essentially in a normal curve on either side of the mean with a slight scattering of some relatively large left axis deviation measurements.

The limits set by twice the standard deviation were 7 to 123 degrees, and only 5 per cent of the records fell outside this range. The limits set by three times the standard deviation were -22 degrees to 152 degrees. Only one record fell above the upper limit of this range, but 2 per cent of the records were less than -22 degrees. These electrocardiograms showed no significant characteristics other than the marked left axis deviation, and the men were all physically fit.

Extrasystoles.—Nine records of this group showed occasional ventricular extrasystoles and three had auricular extrasystoles. The recording of extrasystoles is largely a matter of chance depending upon their frequency and the length of the record. In the short records taken in this series, the above figures on incidence are quite without significance. There were no clinical findings of note in the men who had extrasystoles and no other consistent electrocardiographic peculiarities.

DISCUSSION

Although the human electrocardiogram is relatively constant, it shows considerable variation with respect to the number of deflections and their amplitude and time relations. Certain of these characteristics of the

electrocardiogram have been definitely correlated with cardiac abnormalities. Others are said to occur more frequently in abnormal than in normal hearts, but cannot alone be considered of diagnostic significance in a cardiac examination. The present group of 500 electrocardiograms, which was closely comparable to a previous group of 2,000, show the range of variation in healthy young aircrew trainees. Of this group of physically fit young men, 18 per cent had peculiarities in their electrocardiographic records, which placed them in the doubtful or definitely abnormal categories according to present standards. An additional number of records showed less important variations from the defined normal, such as, extremes of wave amplitude, negative P waves, extrasystoles, etc. When 15 to 20 per cent of normal healthy young men have electrocardiograms which fall in the abnormal class, the definitions of electrocardiographic abnormality require revision, or a careful study is needed to determine whether these same men may later develop cardiac disease. Since the number of apparently abnormal electrocardiograms is so great in young men showing no clinical evidence of cardiac abnormality, and since we have insufficient experience by which to judge the significance of various types of electrocardiographic abnormality in flying personnel, the present system of selection, in which the electrocardiogram is used only as confirmatory evidence in cases showing doubtful clinical evidence of heart disease, seems well justified. A definitely abnormal electrocardiogram alone is not considered sufficient to exclude a man from a flying category if he is fit clinically. However, further experience may show the desirability of taking the electrocardiographic abnormality alone as cause for rejection in certain cases. Since 18 per cent of these men showed definite, if not diagnostic, abnormalities according to present standards, at least an equal number of the men who later claim pension for cardiac disabilities might be expected to show similar findings, and an earlier record will be of great aid in evaluating the significance of the electrocardiographic findings. Routine enlistment electrocardiograms would also be of assistance in confirming the diagnosis when electrocardiographic changes had developed during the period of service.

The limits of amplitude set by twice the standard deviation above and below the mean, corresponded closely with previously accepted standards in the case of the P wave, the upper limits being 1.3, 2.5, and 1.9 mm., in Leads I, II, and III, respectively. However, 3 to 4 per cent of the group showed amplitudes above these limits, with 3 mm. as the maximum limit in Lead II. Consistently negative or diphasic P waves occurred slightly less frequently in Leads I and II of this series than in the group of 2,000 aircrew previously studied, where they were noted in approximately 1 per cent of the records. Three additional records showed occasional negative P waves in auricular extrasystolic complexes. All these negative P waves occurred in the records of perfectly normal men and probably cannot be considered of any sig-

nificance from a clinical standpoint. Negative and diphasic P waves occurred in Lead III in 18 per cent of electrocardiographic records both in this group and in the previous 2,000. This was a considerably larger number than the 3 to 5 per cent reported by Ashman and Hull.[1] Notching of the P waves occurred with such frequency in normal records that it is probably of little significance.

The limits of P-R duration as set by twice the standard deviation above and below the mean were 0.11 to 0.21 second in Lead II. The duration was slightly longer in Lead II than in the other leads. Five per cent of this group of young men had electrocardiograms with P-R intervals beyond this range, half of them showing a prolonged P-R interval by present standards and half a short P-R interval. It cannot be stated positively, of course, that those men with a P-R interval beyond 0.20 second were absolutely normal, or that they will not later show clinical evidence of cardiac disease. However, it can be said that careful clinical and radiological examinations on repeated occasions have shown no significant abnormalities, and that all of the men had cardiac function efficient enough to permit strenuous physical effort in drill and sports. This is equally true of the few men who had P-R over 0.24 second, as of those between 0.21 and 0.24 second, but one must look with somewhat more suspicion on a record with a P-R greater than 0.24 second since they are likely to occur only about three times in a thousand normal individuals.

The significance of a deep Q wave in the absence of other electrocardiographic abnormalities is not clear. Pardee and Price[11] list it as one of the abnormal characteristics of the ventricular complex which, they show, are related in a large percentage of cases to pathologic changes of the myocardium or to the anginal syndrome.[10] Two to 3 per cent of the group of five hundred showed deep Q waves according to present standards with no clinical or other evidence of cardiac disfunction. A follow-up of these cases may prove of interest.

The limits of R-wave amplitude in this group correspond closely to present standards. A range of 6 to 22 mm. includes 95 per cent of the group, and 2 to 26 mm. constitutes the extreme limits with only occasional measurements extending beyond this range in normal young men.

The frequency distribution of the Q and S waves differs considerably from the normal curves evidenced by other complexes and time intervals. Both appear like half of a normal curve with maximum incidence at zero. The greatest amplitude of the Q wave was approximately 4 mm., and that of the S wave, 9 mm.

Slurring or notching of the QRS complex occurred with such frequency in Lead III (26 per cent) in these records that it cannot be considered of much significance. It also occurs in approximately 3

per cent of records in Leads I and II without any definite correlation with other electrocardiographic abnormalities, although a few cases occurred with a borderline or slightly widened QRS interval. It is stated that records with a splintering or slurring in two leads, one nearer the apex than the other, is indicative of an abnormality. Some of these records showed this characteristic, but the percentage of the total group was small.

Fewer negative or diphasic T waves were noted in Leads I and II of this series of 500, than in the 2,000 men previously studied. However, an examination of this characteristic in a further group of 2,000 records taken after the present 500 again showed that 0.5 to 1 per cent of the records had negative or diphasic T waves in Leads I and II. A number of these records are discussed in a later report.[8]

As in the case of the apparently prolonged P-R intervals, it cannot be stated with certainty that the individuals showing negative or diphasic T_1 or T_2 have normal hearts, but there was no clinically determined abnormality in any of them and they made an excellent physical response to effort at the time these records were taken. Electrocardiograms of this type were found in the youngest men of the group as well as among those over 25 years.

The likelihood of coronary occlusion occurring in young men below 25 years of age is debated, and the significance of electrocardiographic characteristics usually considered typical of impaired or decreased coronary blood flow is also in doubt. One airman, not in this series,[8] had negative T waves in Leads I and II, and later died, after a period of active flying service overseas, of what was diagnosed as "acute heart failure." Others who showed this electrocardiographic characteristic are being carefully followed up to determine whether the incidence of coronary lesions may be higher than in other groups.[8] It is probable that, even in young men of apparently excellent health and physical condition, persistently negative T waves in Leads I or II may be sufficient evidence of disturbed cardiac function to justify elimination from aircrew training. There were no consistent changes in the RT-ST segment in the records showing negative T waves, but, as has been mentioned, a small number of other records showed an elevation or depression slightly greater than the standard limit of 1 mm. It may be that this limit should be increased to 1.5 mm. before being considered significant, but the men who had electrocardiographic records with an RT-ST segment above or below the 1 mm. limit are being followed up to determine whether any clinical evidence of cardiac disease may develop. The range of amplitude of T_2 was 1 to 6.6 mm. as set by twice the standard deviation, and 0 to 8 mm. as set by three times the standard deviation from the mean. This suggests that the usually accepted standard of 6 mm. as an abnormally high amplitude might be revised upward to 8 mm. since 3.8 per cent of these normal young men had T-wave amplitudes in excess of 6 mm.

In this group, the average duration of the electrical impulse resulting from ventricular systole was 0.38 second as measured by the Q-T time corrected for variations in cardiac rate. The range of the corrected Q-T period extended to 0.44 second, and almost 40 per cent of the records exceeded the standard of 0.392 second, which is at present accepted as the upper limit of normal.

A relatively large number of records showed right or left axis deviation, 17.2 per cent according to the standards of the Criteria Committee of the New York Heart Association,[3] which set 30 to 90 degrees as the limits of the normal range. According to White[12] the normal limits are 0 to 90 degrees, and by this method a right axis deviation is present if S_1 exceeds R_1. However, left axis deviation is present only if S_3 exceeds R_3 to a more marked extent and R_1 minus S_1 is also relatively large. When the methods defined by the Criteria Committee are used, both right and left axis deviation seem to be measured by the same standards since an S_3 even slightly greater than R_3 then places a record in the left axis deviation group. It would appear, however, from the present analysis, that the normal range should be widened in the direction of the right axis deviation rather than narrowed from the left axis side to 30 degrees. A range of 0 to 120 degrees would include all but 5 per cent of normals, and the limits of –25 to +150 degrees would be necessary to include all but 0.3 per cent of the normals.

This does not mean that all measurements of the deviation of electrical axis within these ranges will be normal, but that the observer who states that they are abnormal without additional proof will have to accept the responsibility for at least a 5 per cent chance of error if the measurement is beyond the 0 to 120 degree range, and up to a 20 per cent chance of error if he accepts the 30 to 90 degree range. Of course, he may be perfectly willing to do this. Any observer can select his own standard of accuracy. However, when the limits are as narrow as those referred to above, i.e., White 0 to 90 degrees, Criteria Committee of the New York Heart Association 30 to 90 degrees, and Ashman and Hull 40 to 90 degrees, the observer must realize that he will be wrong in his decision as to normality or abnormality in 15 to 25 per cent of the cases. As has already been pointed out, the group of men showing left or right axis deviation was clinically normal in all respects in so far as could be determined.

There are two definite types of so-called axis deviation, an apparent deviation in which the position of the heart is changed in its relation to the hypothetical triangle representing the three electrocardiographic leads. Changes can be made to occur in axis deviation by posture or respiration, rotating or moving the heart with relation to this triangle. In some cases, too, the heart may be fixed in the chest so as to give the same effect as a change produced by deep inspiration, as in a tall, narrow-chested person. This type of electrocardiogram cannot be

considered as abnormal even if the axis deviation goes well beyond the accepted normal limits. The second type of axis deviation is definitely abnormal. In this the alteration of wave complexes is produced by a definite right or left ventricular hypertrophy or by bundle branch block in which the electrical waves of the two ventricles are not superimposed in the normal manner. In the former, additional evidence of the abnormality will probably be shown radiologically or clinically, and in the latter the electrocardiogram will in most cases also show a definite conduction defect. Borderline cases, of course, will exist in both groups. In the present series of 500 there were no cases which fell into the second grouping. All were proven normal clinically and radiologically. Although we have no definite evidence of the relationship of these axis deviations to position of the heart, we must assume that the apparent deviations were due to what may be called anatomic variations rather than pathologic ones. As is shown in a later report, some of these records with axis deviation could be changed to normal by a change in posture.

SUMMARY AND CONCLUSIONS

A statistical analysis is presented of the complexes of 500 electrocardiograms taken on Royal Canadian Air Force aircrew. The direction and mean amplitude of the complexes, the standard deviation from the mean and the limits of the distribution as set by two or three times the standard deviation is reported for healthy young adult males between the ages of 18 and 32 years.

P Wave.—The upper limits for the P wave, set by twice the standard deviation, were found to be 1.3, 2.5, and 1.9 mm., in Leads I, II, and III, respectively. Three to 4 per cent of the group showed amplitudes above these limits, with 3 mm. as the maximum limit in Lead II. Although the majority of P waves formed a rounded summit, a considerable number showed a sharp or pointed P wave, and over 5 per cent were notched in varying degrees at the apex.

P-R Interval.—The limits of P-R duration as set by twice the standard deviation were 0.11 to 0.21 second in Lead II, the duration being slightly longer in Lead II than in the other leads. In this group, 5 per cent of the electrocardiograms had P-R intervals beyond this range; 2½ per cent were less than 0.11 second and 2½ per cent greater than 0.21 second in duration.

QRS Complex.—Slurring or notching of the QRS complex occurred in approximately 3 per cent of the records in Leads I and II, and a few of these occurred with a borderline or slightly widened QRS interval. In Lead III this occurred much more frequently and was noted in 26 per cent of the records.

In Lead I, a Q wave was present in 29 per cent of the records, in Lead II in 58 per cent of the records, and in Lead III in 61 per cent of the records. Two to 3 per cent of the 500 records showed deep Q

waves according to present standards. In these cases there were no other significant electrocardiographic abnormalities and the men were clinically normal in all respects. The greatest Q-wave amplitude was 6 mm.

The limits for the R-wave amplitude set by twice the standard deviation were 1.2 to 12 mm. in Lead I, with 3.8 per cent beyond this range; 6.1 to 22 mm. in Lead II, with 5 per cent beyond this range, and 0 to 18.7 mm. in Lead III, with 1.2 per cent beyond this range. The limits of R-wave amplitude in this group correspond closely to present standards. A range of 6 to 22 mm. included 95 per cent of the records.

In approximately 75 per cent of the records, an S wave was present with a mean amplitude of 2.5 mm. The Q and S waves did not show a normal curve of distribution; consequently, standard deviation from the mean was not calculated. The majority of S waves were 1 to 3 mm. in amplitude, with a maximum of 9 to 10 mm. in three records.

The upper limit of QRS time, in this series, set by twice the standard deviation, corresponds with the usually accepted limit of 0.10 second. In Lead I the QRS intervals did not exceed this limit, in Lead II five records had QRS intervals in excess of 0.10 second, and in Lead III six records.

Axis Deviation.—The limits of range for axis deviation set by twice the standard deviation were 7 to 123 degrees, and only 5 per cent of the records fell outside this range.

T Wave.—The limits for T-wave amplitude set by twice the standard deviation were 1 to 5 mm. in Lead I, with 3.4 per cent beyond this range; 1 to 6.6 mm. in Lead II with 3.8 per cent beyond this range, and -1.4 to 3.4 in Lead III, with 4.2 per cent beyond this range. The curve of distribution was normal with less than 5 per cent T waves outside the limits of twice the standard deviation. Twenty-eight per cent of the records showed diphasic or negative T waves in Lead III but only one record had diphasic T waves in Lead II.

RT-ST Segment.—Elevation of the RT segment greater than 1 mm. occurred in Lead I in one record, and in Lead II in five records, but in Lead III there were no records with an elevation greater than 1 mm. Depression of the segment greater than 1 mm. was noted in Lead III only, in three records.

In Lead I slight elevation of segment (77 records) were much more common than depressions (two records, 0.5 mm.), whereas in Lead III depression (0.79 mm.) was more frequent (79 records) than elevation (24 records, 0.6 mm.).

CONCLUSIONS

In general, it may be stated that the range of variation in the electrocardiograms of normal young airmen is considerably greater than the present standards would lead one to expect, and a relatively large

number of records show characteristics which hitherto have been considered diagnostic of heart disease.

Further follow-up studies are required to evaluate the significance of these findings over a period of years. At present, there is no evidence that a healthy young man should not be permitted to continue flying even if he shows what is now considered to be a definite electrocardiographic abnormality, although a follow-up study now being made may show that certain electrocardiographic findings alone should be considered as cause for rejection from aircrew. It would seem, however, that the value of routine electrocardiograms of service personnel may be more valuable for comparative purposes in future pension cases than in primary selection, although they are of definite confirmatory value in the enlistment examination of a number of men with doubtful clinical findings of a cardiac nature.

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ANALYSIS OF THE ELECTROCARDIOGRAMS OBTAINED FROM 1000 YOUNG HEALTHY AVIATORS

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DURING the course of some investigations[1] on a group of Civil Air Line pilots, the electrocardiographic findings proved to be of more than passing interest because of the relatively large number of deviations from the values generally regarded as being normal. Because of their relatively frequent occurrence in the records from apparently healthy persons, it was not easy to believe that all of these deviations declared some underlying cardiac abnormality. The opportunity to extend this study came a year later when electrocardiograms were obtained from a large number of young aviators at the Naval Air Station, Pensacola, Florida. Although the primary purpose of this study is to add to our knowledge of the range of the normal electrocardiogram, some attention is also given to an appraisal of the usefulness of electrocardiography in aviation medicine.

SUBJECTS AND PROCEDURE

All of the 1,000 subjects were males. Eighty-five were advanced student aviators in one of the government sponsored training programs; all the rest were Naval Aviators or Student Naval Aviators. They ranged from 20 to 30 years of age, with a mean of 23.7 years. Approximately 77 per cent were within 10 per cent of the Navy standard of height-weight relationship; 18.4 per cent were overweight, and 4.3 per cent underweight. They were originally selected for flight training only after meeting the most exacting physical requirements, and, in addition, each subject received a careful physical examination at the time our studies were made. All were in good health and none had any signs or symptoms of heart disease.

All of the electrocardiograms were obtained with the subject in the recumbent position and, with a small number of exceptions, in the basal state. Leads IV F and IV R were obtained in addition to the

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This work was carried out under a special grant from the Civil Aeronautics Administration to the National Research Council Committee on Selection and Training of Aircraft Pilots, and permission has been obtained from this Committee to publish these results.

The views and opinions expressed in this paper are those of the authors and are not necessarily the views of the organizations mentioned above.

standard three leads. The electrodes and lead wires were so adjusted that after recording Lead IV F, Lead IV R could be obtained by simply turning the lead-selector switch; thus, the conditions were identical during the recording of both precordial leads.

Sanborn electrocardiographs (cardiettes) were used throughout the study. The timing device was repeatedly checked for accuracy, and all of the instruments were returned to the factory for overhaul at least once during the study. More than ordinary care was taken in the procuring and developing of the records.

The various measurements obtained from the electrocardiograms were carefully made. A magnifying lens was used in determining the duration of the QRS complex and sometimes in measuring the amplitude or duration of other deflections. The data obtained were all recorded on master sheets and the statistical analysis made from these figures.

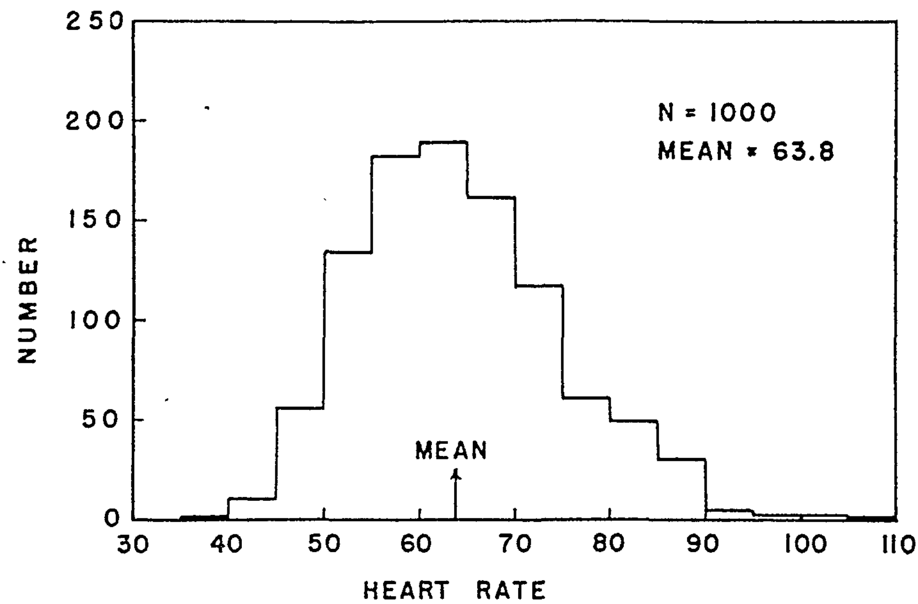


Fig. 1.—Range and distribution of heart rates.

THE HEART RATE

The heart rate was determined from the electrocardiogram by taking the average of three or four measurements of 6 seconds each. The range was from 38 to 110. The mean heart rate was 63.8 and the mode 62. The histogram in Fig. 1 shows the distribution, and it is noteworthy that in only three instances was the heart rate above 100. The mean heart rate of the subjects in this series is nearly the same as that found by Robinson[2] and by Brouha and Heath[3] in their groups of young subjects who were examined in the basal state, and by McFarland, et al.,[1] in a group of civilian pilots.

RHYTHM

Normal Rhythm.—In the study of the electrocardiogram, normal rhythm is defined as a nearly regular sequence of beats between the

rates of 60 and 100* in which the excitation impulse arises normally in the S-A node and is conducted normally throughout the heart. All other rates and rhythms have a special name and are often grouped under the "disorders or disturbances of rhythm."

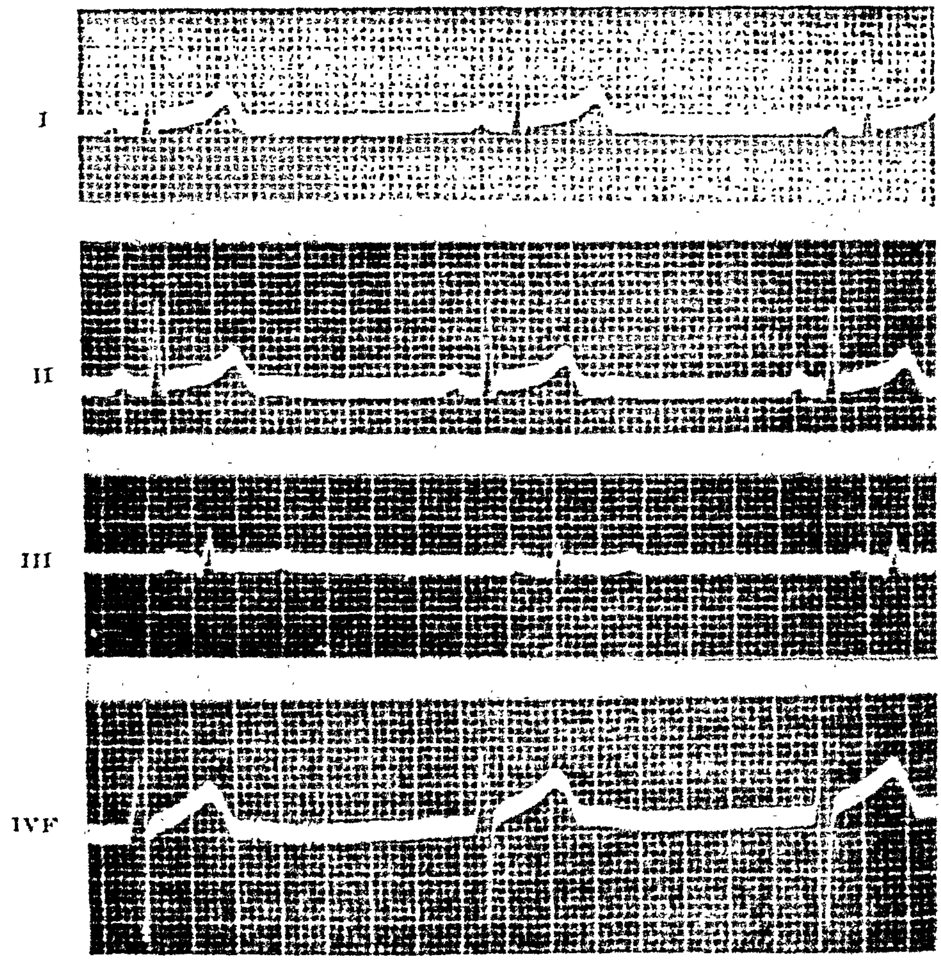


Fig. 2.—S-A bradycardia (rate 38).

Sinus Bradycardia.—Heart rates between 50 and 60 were very common and almost a third (315) of our subjects had rates within this range, and more than one-third (382) had rates below 60. It is perhaps unfortunate that such narrow limits have been set with regard to heart rate in defining normal rhythm. The term sinus bradycardia might more properly be reserved for rates below 45. The extreme S-A bradycardia (rate 38) observed in one case (Fig. 2) is of interest because it is one of the few examples on record[4] of a heart rate slower than 40 beats a minute in a healthy well-nourished person.

Sinoauricular Tachycardia.—Three of our subjects had heart rates between 100 and 110. While it has been shown[5] that young, healthy, well-trained athletes at rest have pulse rates above 100, tachycardia of this degree should be regarded with suspicion.

*This is the range adopted by the American Heart Association

Sinus Arrhythmia.—No especial attention was given to this arrhythmia, but in 56 instances it was sufficiently pronounced for a notation of its presence to be made.

Variations in the Location of the Pacemaker.—There were 23 instances of *wandering of the pacemaker* in and about the S-A node. These were all characterized by variations in the form of the P waves and with the P-R interval remaining unchanged. This unimportant form of arrhythmia has no pathologic significance. A single instance was observed of *S-A block with A-V nodal escape.* This too has no pathologic connotation. There was one example of A-V nodal rhythm with short P-R interval (0.09 second) and inversion of the P waves in Leads II and III. The rhythm was regular at a rate of 77 a minute. Although nodal rhythm may result from heart disease, it is usually to be regarded as a disturbance of rhythm which neither causes symptoms nor is associated with diseases of the heart. The above instance is unusual in that the rate is relatively rapid, which indicates a heightened irritability of the A-V node more than depression of the S-A node.

Short P-R Interval and Wide QRS Waves.—There were two examples (Figs. 3 and 4) of this curious arrhythmia, first described by Wolff, Parkinson, and White.[5] Recent studies[6] have shown that it may be the result of an anamolous connection between the auricles and ventricles. Because persons with this anomaly are prone to have attacks of paroxysmal tachycardia, its presence should disqualify a candidate for flight training. The discovery of two cases in 1,000 may not represent its true incidence but does suggest that it occurs sufficiently often that it must not be neglected.

Premature Beats.—The electrocardiograms in fifteen instances showed premature beats; eight were of the ventricular and seven of the auricular variety. The actual incidence of premature beats in our subjects was probably many times greater than we observed, as the recording time was short. Although the number of cases observed is too small to be of statistical significance, yet it is of a little interest that in this young, healthy group there were nearly the same number of auricular as ventricular premature beats. The latter are ordinarily regarded as occurring three or four times as frequently as the former.

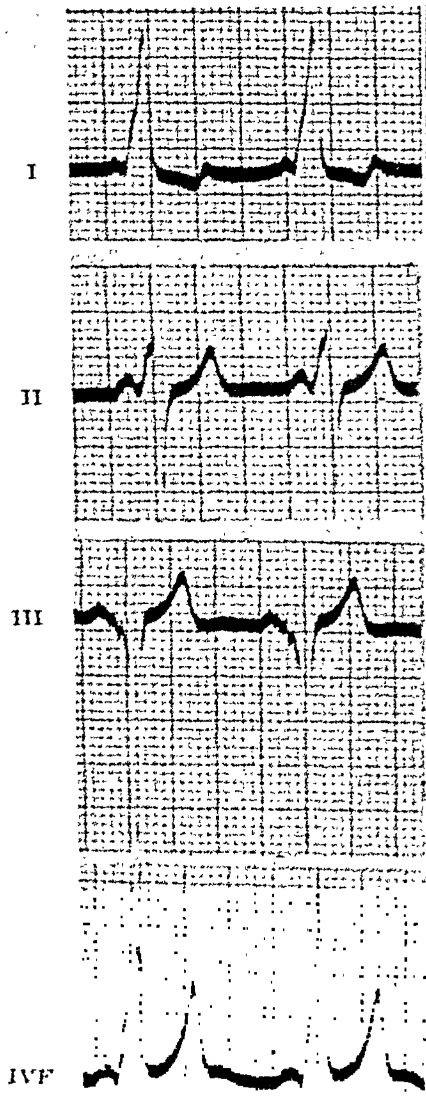
Heart Block.—There were sixteen instances of the so-called first stage of heart block or prolongation of the A-V conduction time beyond 0.20 second. This will be discussed below under P-R Interval.

Intraventricular Conduction Defects.—There were 38 electrocardiograms in which the duration of QRS was more than 0.10 second. These will be discussed under QRS Complex below.

THE P WAVES

The duration, amplitude, and form of the P waves were determined in the three standard leads. The duration of P was measured from the point on the lower edge of the base line at which it left the

zero level to the point of return. The amplitude was measured from the upper or lower edge of the base line to the peak, respectively, according to whether P was upright or inverted. The forms of the P wave were classed as follows: pointed, rounded, notched, and diphasic.



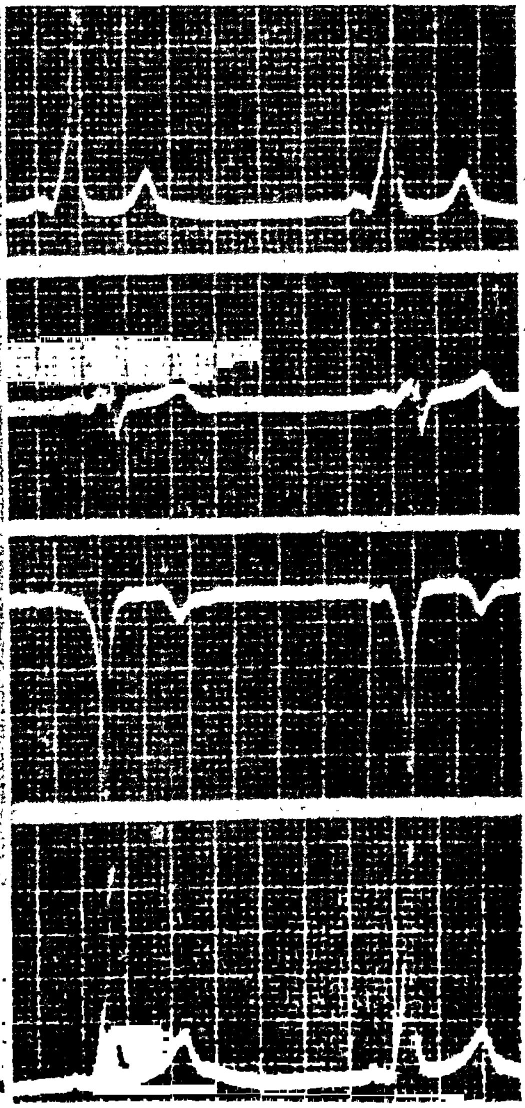


Fig. 3.—Short P-R and wide QRS. Fig. 4.—Short P-R and wide QRS.

Duration of P.—The values for the entire range of the duration of P are shown in Table I. Particular interest centers in the extremes. P waves were always observed in Lead II and were absent in only one instance in Lead I and one in Lead III. When the P waves in one or other of the three leads were tiny, the duration was *correspondingly* short. P waves of more than 0.1 second duration were observed only occasionally.

Amplitude of P.—Table II shows the range of the amplitude of P except in three instances of abnormal rhythm. In Lead I, P was seldom

TABLE I

DURATION OF THE P WAVE IN THE STANDARD LEADS

DURATION OF P (SEC.)	PERCENTAGE		
	LEAD I	LEAD II	LEAD III
0.00	0.1	–	0.1
0.01	–	–	0.1
0.02	0.3	0.1	0.4
0.03	0.7	0.2	0.6
0.04	6.9	1.0	6.3
0.05	4.5	0.4	5.6
0.06	18.5	4.3	22.4
0.07	11.5	6.3	15.1
0.08	37.5	35.3	35.2
0.09	9.3	25.8	8.4
0.10	9.4	22.2	4.4
0.11	1.0	2.9	0.9
0.12	0.3	1.5	0.5
Mean Duration	0.074	0.086	0.073

TABLE II

AMPLITUDE OF THE P WAVE IN THE STANDARD LEADS

AMPLITUDE OF P (MM.)	PERCENTAGE		
	LEAD I	LEAD II	LEAD III
-0.9 to -2.0	–	–	0.4
-0.5 to -0.8	–	0.1	3.8
-0.1 to -0.4	–	–	2.7
0	–	–	0.1
0.0 to +0.3	13.4	2.3	8.0
+0.4 to +0.7	57.9	16.4	29.2
+0.8 to +1.1	26.8	38.1	29.2
+1.2 to +1.5	1.4	33.9	8.8
+1.6 to +1.9	–	4.9	0.6
+2.0 to +2.3	–	1.6	0.4
+2.4 to +2.7	–	0.4	0.1
+2.8 to +3.0	–	0.1	–
Diphasic (+ –)	0.5	1.3	14.1
Diphasic (– +)	–	0.9	2.5

more than 1 mm. in amplitude and was never actually inverted; in five instances P was diphasic. In Lead II, P was seldom greater than 2 mm. in amplitude, was occasionally diphasic, and actually inverted in only one instance. In Lead III, P was seldom more than 1.5 mm. in amplitude, was often diphasic and sometimes inverted. It is noteworthy that when P was diphasic, the upright preceded the downward phase in all but three instances.

Form of P.—Table III shows the various forms of P observed in the three standard leads. The distinction between rounded and pointed was made arbitrarily on the basis of whether the summit of P was part of a curve, or a peak. All degrees of notching are included under "notched," which accounts for the large frequency of notched waves. However, it again serves to emphasize the fact that notching is very commonly found. Diphasic P waves were rarely found in Leads I and II but were commonly found in Lead III.

TABLE III

FORM OF THE P WAVES IN THE STANDARD LEADS

FORM OF P	PERCENTAGE		
	LEAD I	LEAD II	LEAD III
Apex rounded	49.8	29.4	28.4
Apex pointed	22.3	41.1	25.8
Notched	27.5	28.2	26.3
Diphasic	0.5	1.6	16.1

P-R INTERVAL

The P-R or P-Q interval was determined by measuring from the beginning of the P wave to the beginning of the QRS complex. This measurement was made in Lead II except in occasional instances where the P waves were poorly defined or where P-R was of longer duration in another lead. The P-R interval was found to vary in duration from 0.09 to 0.28 second, and the mean was 0.154. In all but 82 instances the P-R varied between 0.12 and 0.18 second as shown in Table IV. This requires no further comment because these values are well within the generally accepted range for healthy young adults.

The P-R interval was 0.11 second in six instances, and 0.10 in seven others; in two of the latter (Figs. 3 and 4), the QRS complexes were abnormally wide as described above. The P-R interval was 0.09 second in the one instance of A-V nodal rhythm. An example of short P-R with normal QRS is shown in Fig. 5. The impulse passes with unusual rapidity from auricles to ventricles, and there is, presumably, less delay than ordinarily in the junctional tissue surrounding the A-V node.

TABLE IV

DURATION OF THE P-R INTERVAL

P-R INTERVAL (SEC.)	NUMBER OF INSTANCES
0.12	76
0.13	83
0.14	211
0.15	117
0.16	249
0.17	95
0.18	84
	Total = 915

The P-R interval was 0.19 second in 19 instances and 0.20 in 33 instances. Although these values are within the usually accepted normal range, it is worth remarking that these values occurred infrequently. Of greater significance was the finding of P-R intervals of 0.21 second in four instances, 0.22 second in eight instances, and one instance each where the P-R interval was 0.24, 0.25, 0.26, and 0.28 second. There was no evidence of rheumatic fever in any of these cases, and careful examination did not disclose any infection or other abnormality. Unfortunately, we were not able to observe these cases for longer than a few days. Other investigators, likewise, have occasionally

observed abnormally long P-R intervals in otherwise healthy persons. Thus, Ferguson and O'Connell[7] found the P-R interval to be longer than 0.20 second in over 1 per cent of the electrocardiograms from 1,812 healthy young men. Hall, Stewart, and Manning[3] likewise observed the P-R interval to be over 0.20 second in nearly 2 per cent of the electrocardiograms from 2,000 apparently healthy persons. Thus, although P-R intervals greater than 0.20 second should raise the question of past or present heart disease, they may indicate neither.

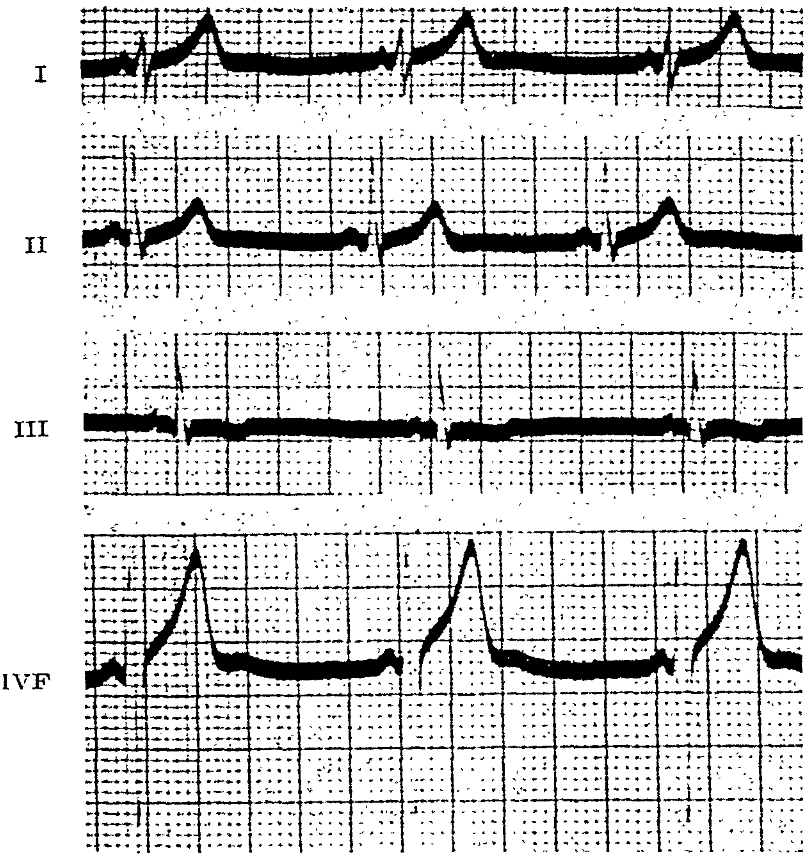


Fig. 5.—Short P-R and normal QRS.

The P-R interval is known to vary with the length of the cardiac cycle or heart rate; this relationship is shown in Table V. P-R intervals longer than 0.20 second were not found at heart rates of 80 or above.

QRS COMPLEX

Before proceeding to the description of the QRS findings, it is necessary to mention the terminology used and the manner in which the several waves were measured. The present study was begun prior to the appearance of a report on electrocardiographic terminology made by the Committee for the American Heart Association,[9] but the terminology used here does not vary very much from that recommended. A single upstroke is called R, any preceding downstroke Q, and any following downstroke S. All other forms are separately described as follows: in the absence of Q as defined above, a heavy slurring at the base line on the upstroke of R is termed a "fused Q wave." If a tiny upstroke

TABLE V

VARIATION IN THE P-R INTERVAL WITH HEART RATE

RATE	NUMBER	P-R INTERVAL CORRELATED WITH HEART RATE	
		MEAN (SEC.)	RANGE (SEC.)
40-49	60	0.159	0.12-0.20
50-59	315	0.157	0.10-0.28
60-69	349	0.153	0.10-0.25
70-79	174	0.152	0.11-0.24
80-89	76	0.144	0.09-0.20
90-99	13	0.145	0.12-0.18

TABLE VI

DURATION OF QRS

DURATION OF QRS (SEC.)	NUMBER OF INSTANCES
0.06	7
0.07	68
0.08	431
0.09	295
0.10	161
0.11	27
0.12	8
0.13	1
0.14	2
	Total = 1,000

precedes Q, it is considered part of that wave and described separately. The same terminology applies to S. A QRS complex of low amplitude consisting of several waves is termed a "vibratory QRS complex."

The duration of QRS was measured in the lead giving this wave the greatest value. The amplitude of Q and S were determined by measuring from the level of the lower margin of the P-Q segment to the apex of the wave, and the level of the upper margin was used in the case of R. Notching refers to a definite spike, and slurring to a definite thickening, more than 2 mm. from the base line on one of the limbs of Q, R, or S which has an amplitude of 5 mm. or more.

Duration of QRS.—The duration of QRS was found to vary from 0.06 to 0.14 second with a mean value of 0.087; Table VI gives the figures for the entire range. It is of interest to compare these findings with those of other investigators.

The duration of QRS was measured by McGinn and White[10] with the aid of a Lucas comparator and was found to average 0.0833 second in 50 adult males of all ages, and 0.0722 in 50 females. Earlier studies reported similar average values but were based on smaller series of cases. Shipley and Halloran[11] obtained average values of 0.087 second for males and 0.085 second for females in a series of 200 cases. Lüderitz[12] found the average duration of QRS to be 0.080 second in 500 cases. The values obtained by Haskin and Jonescu[13] were extraordinarily small, due to the manner in which they measured the QRS duration.

The *range* of the QRS duration is of far greater importance than the *average* value because at the upper extreme there is considerable overlap with the abnormal. Practically all of the early electrocardiographers, beginning with Lewis, considered 0.10 second as the upper normal limit. Here again, the conclusion was based on the study of a small series of cases. Ferguson and O'Connell[7] reported finding the QRS longer than 0.10 second in two tracings from 1,812 healthy young men. McGinn and White[10] observed three instances in 100 where the duration of QRS was between 0.10 and 0.11 second. Shipley and Halloran[11] observed the duration of QRS to be 0.11 second in two instances and 0.12 in one, in their series of 200 cases. Lüderitz[12] discovered the QRS duration to be 0.11 second in nine and 0.12 in two instances among 500. Chamberlain and Hay[14] did not observe any QRS waves longer than 0.10 second, but their observations in this regard were limited to Lead II, whereas the duration of QRS is often greater in Lead III or even in Lead I. Haskin and Jonescu,[13] in a study of 50 normal women, found the longest duration of QRS to be 0.09 second. Ashman and Hull,[15] in their series of 100 cases, did not find any QRS waves longer than 0.10 second, and Hall, Stewart, and Manning,[8] in an analysis of 2,000 records, found only two showing QRS waves greater than 0.10 second. It is readily seen from these reports that QRS waves in the standard leads greater than 0.10 second in duration are rarely encountered in the electrocardiograms from healthy persons. Inasmuch as a diagnosis of "normal" heart cannot be made with finality in the living, and the fact that there are occasional cases showing a considerable degree of coronary arteriosclerosis at an early age, the evaluation of these unusual records is difficult. Because of the interest in, and importance of, this problem, it seems worth while to discuss in more detail the cases in our series where QRS was found to be greater than 0.10 second in duration.

In 27 instances (2.7 per cent) QRS measured 0.11 second. In every case it was found that this measurement was obtained in a lead plainly showing Q, R, and S. In other words, it was unlikely that any portion of this complex was isoelectric and "buried" in the base line. In most of the 27 instances a casual glance at the record might not immediately raise the suspicion that QRS was unusually long; the form of the ventricular components did not appear abnormal. It was only after careful measurement that the QRS was discovered to be prolonged. It is our opinion that if the full duration of QRS can be observed, and if it is carefully measured, durations longer than 0.10 second will occasionally be found in the records from healthy males. Thinking in terms of the laws of probability, it seems unlikely that 27 subjects in our series had heart disease interfering with the conduction of the excitation wave through the ventricles.

There were eight instances in which the duration of QRS was 0.12 second. In seven of these eight, the form of the S-T segments and T waves was normal, and the only unusual feature was the extraordinary length of QRS. Examples of this are shown in Figs. 6 and 7. The remaining instance (Fig. 8) shows typical left bundle branch block with the T waves oppositely directed to the chief initial ventricular deflection in Leads I and III. This record was obtained from a Naval Aviator, aged 29 years. He was studied and tested in the most thorough manner but no evidence of heart disease was discovered. His progress was followed for two years (until the onset of the War) and he remained in good health. The cause of the conduction defect in this case is not known but it is not unreasonable to suppose that, rarely, even in young, apparently healthy persons, congenital anomalies of the conduction system, or injury from localized inflammation, or disease of the nutritive artery, may be responsible.

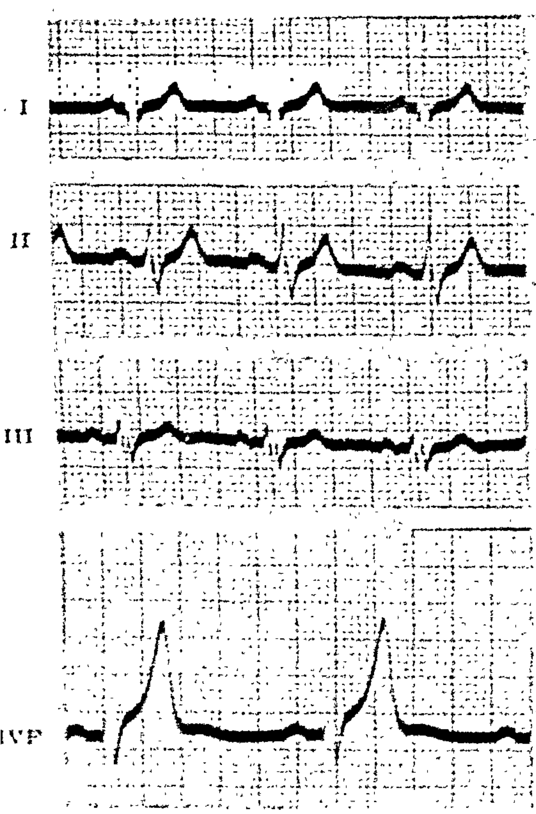


Fig. 6.—QRS = 0.12 second.

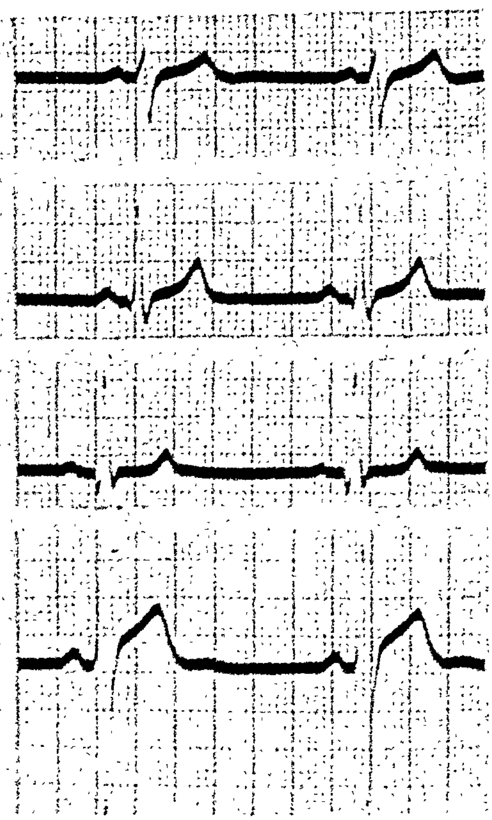


Fig. 7.—QRS = 0.12 second.

Another interesting example is seen in Figs. 9 and 10. These tracings were obtained from a student Naval Aviator, 24 years of age. The record in Fig. 9 was taken with the subject under basal conditions and the record in Fig. 10 was taken a few minutes later after a pistol had been fired near him. The change in intraventricular conduction occurred within 30 seconds of the explosion, and the abnormality remained for

two days. This subject was studied exhaustively but no evidence of heart disease or impairment was found. The fact that the faulty conduction occurred as a temporary functional condition is significant. It indicates the possibility that all disturbances of intraventricular conduction need not be explained on an anatomic basis.

There was one instance where the duration of QRS was found to be 0.13 second; the S-T segments and T waves were not affected. Thorough study and testing did not reveal any evidence of cardiac disorder.

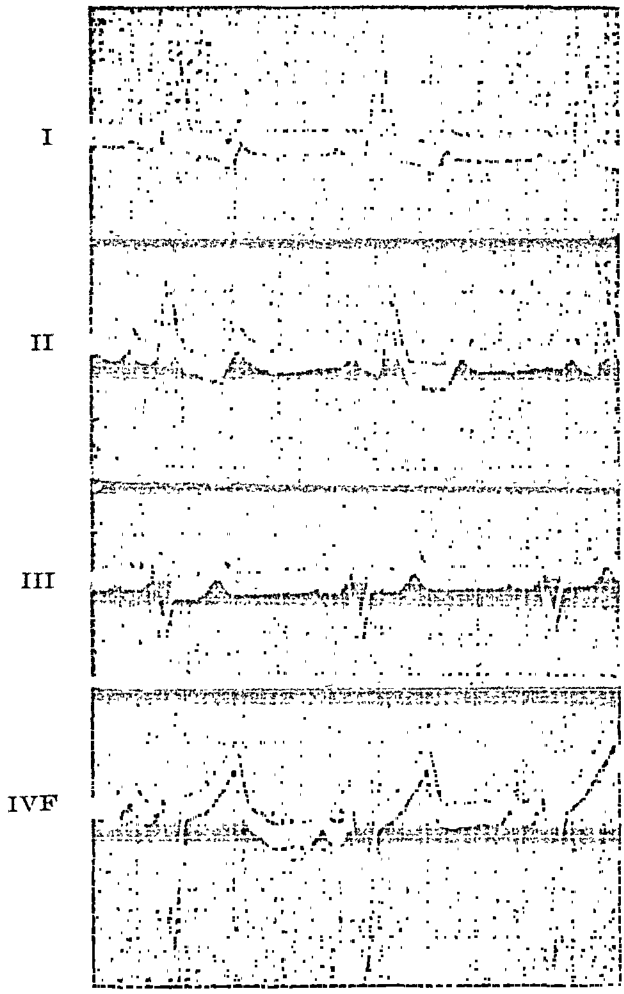


Fig. 8.—Left bundle branch block.

And, lastly, there were two instances of wide QRS associated with a short P-R interval. This phenomenon and its significance have been discussed above.

While freely admitting the uncertainties with regard to the unusual prolongations of QRS observed in this series, the following conclusions seem to be justified.

1. QRS complexes as long in duration as 0.13 second may be observed in young persons without any evidence of heart disease.

2. A QRS duration of 0.11 second is found with sufficient frequency in young healthy persons to suggest that it is not necessarily of pathologic significance.

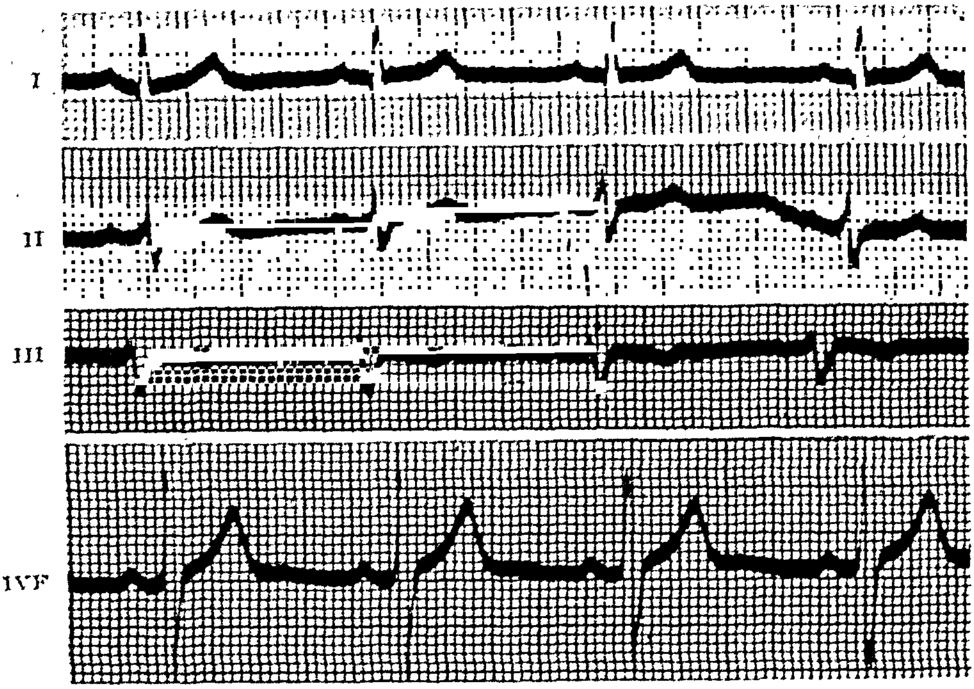


Fig. 9.—Control record.

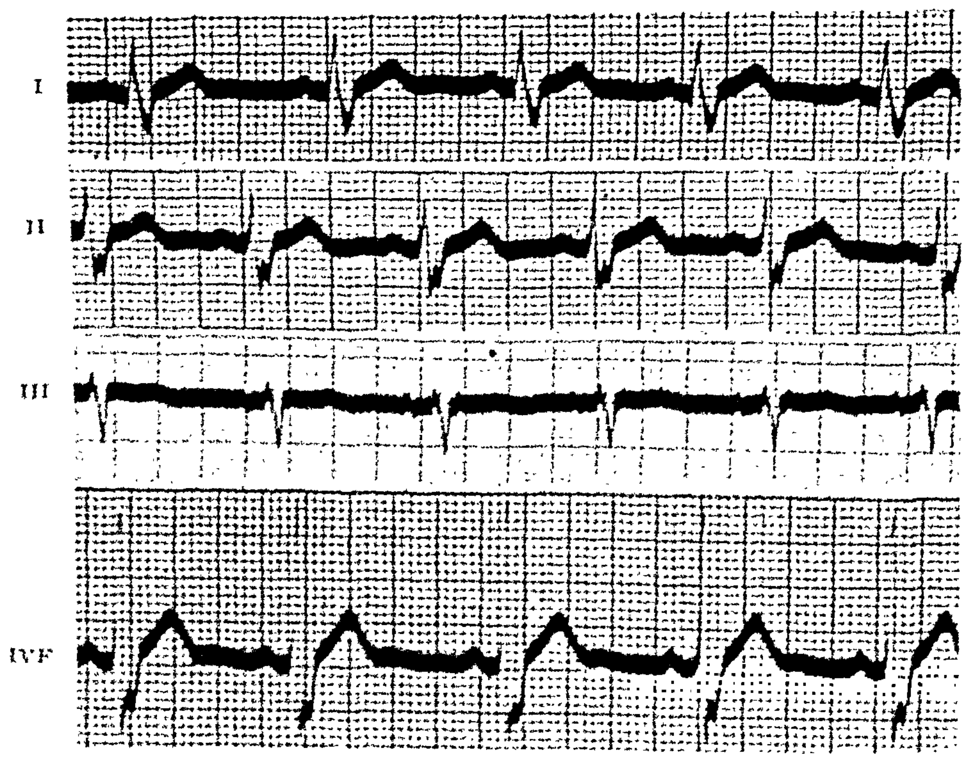


Fig. 10.—After stimulus.

3. QRS complexes of 0.12 second duration, even when observed in the electrocardiograms from young, apparently healthy persons, are usually caused by some abnormality but in rare instances may not have any pathologic signficance.

4. The duration of QRS has been observed to increase temporarily as the result of a fright stimulus.

THE Q WAVE

In Lead I, omitting three records showing abnormal rhythm, there were 511 instances of a definite negative deflection preceding the R, six instances in which a tiny upstroke preceded Q (R^1 new terminology), 23 instances of a heavy slur at the beginning of the upstroke of R (fused Q wave), and 456 instances in which R was not preceded by another wave. The amplitude of Q in the 511 instances where it was a single negative deflection ranged from –0.1 to –3, and the mean was –0.54. The amplitude of Q equalled 7.8 per cent of the amplitude of R_1 on the average, and the range was from 0.8 to 33 per cent. The amplitude of Q_1 equalled 5.6 per cent of the amplitude of the tallest R in any of the three standard leads on the average, and the range was from 0.6 to 25 per cent. Thus, in Lead I, Q was never found to be greater than 3 mm. in amplitude, and it was never more than 33 per cent of the amplitude of the R in that lead or more than 25 per cent of the amplitude of R in any lead. There were only three instances where Q_1 was 20 per cent or more of the tallest R in any lead.

In Lead II there were 681 instances of a definite negative deflection preceding the R, eight instances in which a tiny upright wave preceded the Q (R^1 new terminology), 56 instances of a heavy slur at the beginning of the upstroke of R (fused Q wave), and 260 instances in which R was not preceded by any other wave. The amplitude of Q in the 681 instances where it was a negative deflection ranged from –0.1 to –3.5 and the mean was –0.73. The amplitude of Q_2 equalled 6 per cent of the amplitude of R_2 on the average and ranged from 0.6 to 50 per cent. The amplitude of Q_2 equalled 5.8 per cent of the amplitude of the tallest R in any of the three leads on the average and ranged from 0.6 to 50 per cent. Thus, the maximum amplitude of Q in Lead II was 3.5 mm., but in only three instances was it 20 per cent or more of R in the same lead.

In Lead III there were 677 instances of a definite downward deflection preceding the R, 61 instances where a tiny upright deflection preceded the first important deflection in QRS (R new terminology), 92 instances of a heavy slur at the beginning of the upstroke of R (fused Q wave), 33 instances where the QRS consisted of so many deflections that a definite Q could not readily be identified, and 134 instances in which no Q wave was seen. The amplitude of Q in the 677 instances where it was a negative deflection ranged from –0.1 to –4.5 mm., and the mean

was −1.04. The amplitude of Q_3 equalled 14.8 per cent of the amplitude of R_3 on the average, and the range was from 0.7 to 150 per cent. There were 26 instances where Q_3 was equal to one-half or more of the amplitude of R_3. The amplitude of Q_3 equalled 8 per cent of the amplitude of the tallest R in any of the three limb leads and the range was from 0.6 to 60 per cent. There were 18 instances where Q_3 was equal to one-fourth or more of the amplitude of the tallest R in any lead.

THE R WAVE

In Lead I, omitting the three instances of abnormal rhythm, the R waves were always upright and ranged in amplitude from 1 to 16.5 mm., with a mean value of 5.9 mm. There were 62 instances where R_1 was between 10 and 16 mm. in amplitude.

In Lead 2 the R waves were always upright, ranging in amplitude from 1.3 to 26 mm. and with a mean value of 11.6 mm. There were 152 instances in which the amplitude was from 15 to 19.9 mm., and 29 instances in which it was from 20 to 26 mm.

In Lead III the R waves were upright in 946 instances, ranging in amplitude from 0.5 to 24 mm. with a mean of 7.2 mm. In the remaining 61 instances QRS was described as a vibratory complex or inverted.

THE S WAVE

In Lead I, again omitting the three cases showing abnormal rhythm, there were 856 instances of a definite negative deflection following the R wave, six instances in which there was a tiny upright wave following the last important QRS deflection (R^2 new terminology), 39 instances of a heavy slurring at the end of the downstroke of R (fused S wave), and 99 instances in which R was not followed by another wave. The amplitude of S in the 856 instances where it was a negative deflection ranged from −0.1 to −6.3 mm., and the mean was −1.74 mm. The amplitude of S_1 equalled 39.5 per cent of the amplitude of R_1 on the average, and the range was from 0.9 to 266.7 per cent. The amplitude of S_1 equalled 16.2 per cent of the amplitude of the tallest R in any of the three limb leads on the average, and the range was from 0.5 to 90 per cent. Thus, in Lead I, S waves as great as 6.3 mm. in amplitude were observed, and in 21 instances (excluding records with right axis deviation) S was 4 mm. or more in amplitude.

In Lead II there were 749 instances of a definite downward deflection following the R wave, eight instances in which there was a tiny upright wave following the last important deflection of QRS (R^2 new terminology), 109 instances of a heavy slurring at the end of the downstroke of R (fused S wave), and 138 instances in which S was absent. The amplitude of S in the 749 instances where it was a downward deflection ranged from −0.1 to −9 and the mean was −1.78. The amplitude of S_2 equalled 20.3 per cent of R_2 on the average and ranged from 0.6 to 200 per cent.

The amplitude of S_2 equalled 18.4 per cent of the tallest R in any of the three limb leads on the average and ranged from 0.6 to 143 per cent. Thus, S in Lead II was observed to be as much as 7 mm. in amplitude and was sometimes over twice the amplitude of R_2 and greater than the amplitude of R in any lead (Fig. 11). S_2 was greater than 4 mm. in amplitude in 24 instances, excluding cases of right axis deviation.

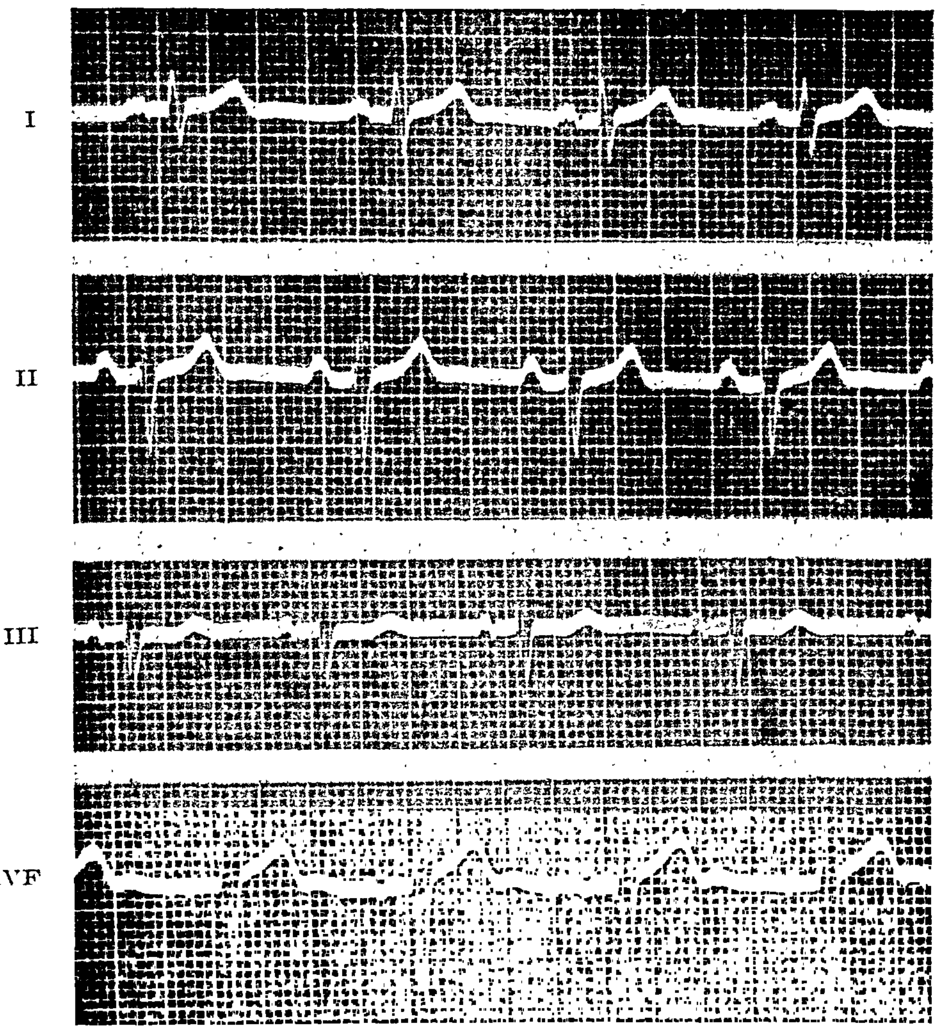


Fig. 11.—Prominent S waves.

In Lead III there were 527 instances of a definite negative deflection following the R wave, 12 instances in which a small upright wave followed the last main QRS deflection (R^2 new terminology), 117 instances of a heavy slur at the end of the downstroke of R, 346 instances in which S was absent or the QRS complex was inverted or vibratory. The amplitude of S in the 527 instances where it was a definite downward deflection ranged from –0.1 to –12 mm. with a mean of –1.48 mm. The amplitude of S_3 equalled 43.5 per cent of R_3 on the average, the range being 0.6 to 500 per cent, and equalled 15.8 per cent of the tallest R in any lead on the average, with a range of 0.6 to 160 per cent. Thus in Lead III, S was found to be as much as 12 mm. in amplitude and as much as five times the amplitude of R in that lead and nearly twice the amplitude of R in any lead.

FORM OF QRS

There was no instance of notching of the Q, R, or S waves in Leads I and II but there was slight slurring of R_1 in 23 instances and R_2 in 35. Slurring and occasional notching were frequently observed near the base line especially when the voltage of the waves was low. In Lead III, R was slurred in 80 instances and notched in 17. A vibratory QRS complex was not observed in Leads I and II, but was observed in 52 instances in Lead III. The QRS complex was "inverted" in 25 instances in Lead III but not in Leads I and II except for the inversion of Lead II associated with left axis deviation.

There were 16 instances where the greatest amplitude of any deflection of QRS in the standard leads was no greater than 5 mm. and 70 instances where the amplitude was from 5.1 to 7 mm. The small incidence of low voltage of QRS in this series contrasts sharply with the much greater incidence found in a smaller but older group of pilots.[1] The large amplitude of QRS in young persons is a well-known fact. An account of the incidence and significance of low voltage may be found in the recent papers of Leach, Reed, and White[16] and Bellet and Kershbaum.[17]

THE ELECTRICAL AXIS

The angle of the electrical axis of the electrocardiogram was calculated according to the method of Carter, Richter, and Greene[18] for all records except those where the QRS duration was greater than 0.11 second. The range was from +120 degrees to −36 degrees and the mean angle was 64.2 degrees. The "normal" axis is sometimes stated to lie between 0 and 90 degrees but many observers have found the extremes to be much greater. From a consideration of the significance of this angle it is apparent that it may vary within wide limits in the electrocardiograms from persons with normal hearts.

Various indices have been proposed as rough guides to the degree of axis deviation and the one used here is that proposed by White,[19] namely, Index = $(R_1 - S_3) - (R_3 + S_1)$. The range was found to be from +23 to −21 and the mean −2.25. White gives the normal range as lying between +30 and −15.

Left axis deviation was considered to be present when the algebraic sum of $R_1 + S_1$ was positive and the sum of R_3 and S_3 was negative, and R_1 was greater than R_2.[20] There were 51 instances in which these criteria were fulfilled. A ratio was obtained by dividing the amplitude of R by the amplitude of S in Lead II; the values ranged from 0.3 to 17 with a mean of 4.17. There were 21 instances of "inversion of Lead III," i.e., the P wave, the chief initial ventricular deflection and the T wave, were all downwardly directed. There were no instances in which the S-T segments were displaced in an opposite direction from the chief initial deflection in Leads I and III.

Right axis deviation was considered to be present when the sum of R_1 and S_1 was negative, the sum of R_3 and S_3 positive, and R_3 was greater than R_2. There were 22 instances in which these criteria were fulfilled. The ratio of R_2/S_2 ranged from 1.1 to 17.6 and the mean was 6.8. There were no instances in which the S-T segments were oppositely displaced from the chief initial deflections in Leads I and III.

In summary, then, it is seen that in young, healthy persons without hypertension and without cardiac enlargement which can be detected by clinical and x-ray examination (A-P teleroentgenogram of chest), the electrical axis of the electrocardiogram may vary within a wide range. In some instances the S waves in Lead II may be as great or greater in amplitude than R, but the S-T and T-wave changes associated with ventricular preponderance are not observed.

S-T JUNCTION AND S-T SEGMENT

The displacement of the S-T junction was measured and the various forms of the S-T segment classified. The S-T junction was considered to be the point of union between the QRS complex and the S-T segment or the T wave and the reference level the P-Q segment. The S-T segment was considered to be (1) ascending, (2) concave, (3) convex, and (4) flat.

TABLE VII

DISPLACEMENT OF THE S-T JUNCTION IN THE STANDARD LEADS

		N	MEAN (MM.)	RANGE (MM.)	NUMBER GREATER THAN 1 MM.
Lead I	upward	854	+0.41	+0.1 to +1.5	5
	none	137			
	downward	9	-0.64	-0.1 to -1.2	1
Lead II	upward	890	+0.62	+0.1 to +2.0	30
	none	98			
	downward	12	-0.46	-0.1 to -1.0	0
Lead III	upward	460	+0.43	+0.1 to +1.5	7
	none	463			
	downward	77	-0.33	-0.1 to -1.5	1

Table VII shows the incidence of the upward and downward displacement of the S-T junction in the three standard leads. The particular points of interest are the rarity with which the S-T segment was downwardly displaced and the fact that occasionally it may be displaced upwardly more than 1 mm. from the base line.

The incidence of the various forms of the S-T segment is shown in Table VIII. It is difficult to describe this segment, and the classification into the various forms is unsatisfactory. This is true for many reasons, including the fact that there are many degrees of variation within a given general pattern, the presence of mixed forms, and the failure to take into account the level of the S-T junction and the form of the T wave.

TABLE VIII

FORM OF S-T SEGMENT IN THE STANDARD LEADS

FORM OF S-T SEGMENT	PERCENTAGE		
	LEAD I	LEAD II	LEAD III
Ascending	13.4	12.9	3.5
Concave	76.9	79.7	45.4
Convex	0.2	0.0	2.3
Flat	9.5	7.4	48.8

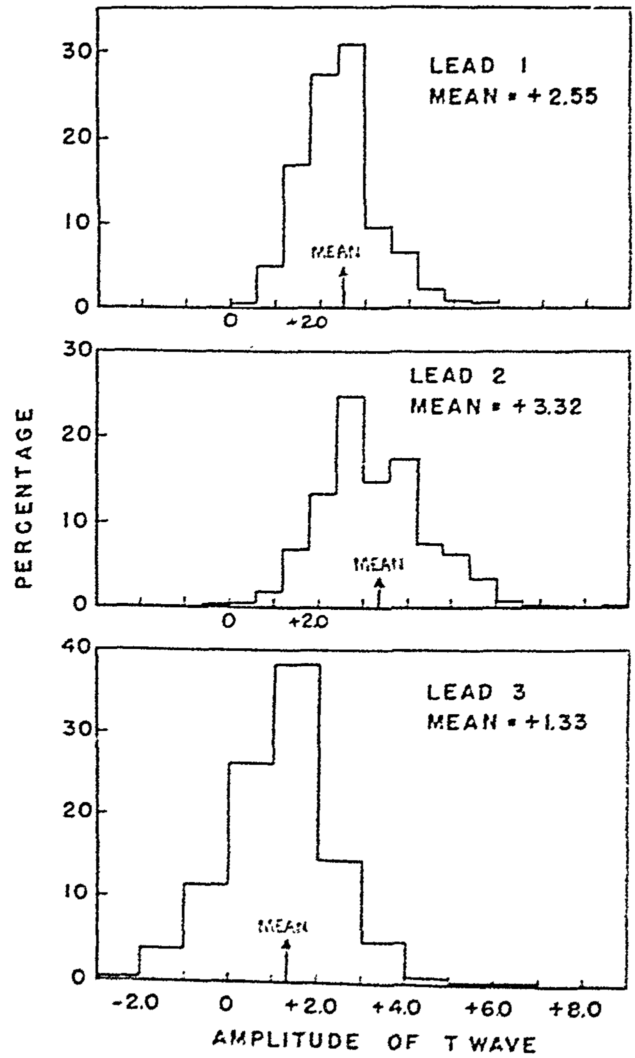


Fig. 12.—Percentage distribution of the various amplitudes of T in the standard leads.

THE T WAVE

The data pertaining to the duration and amplitude of the T waves in the three standard leads is summarized in Table IX and Fig. 12. There was not a single instance of inversion of T in Lead I, omitting the three records with abnormal rhythm, but T was sometimes low (Fig. 13). In Lead II there were only two instances of inversion of T (Figs. 14 and 15), and one of diphasic T. In Lead III, T was inverted or

diphasic in over one-fifth of the records. The T waves in all three leads were not greater than +1 mm. in two records and +2 mm. in 119 records.

TABLE IX

AMPLITUDE OF THE T WAVE IN THE STANDARD LEADS[5]

	N	MEAN (MM.)	MODE (MM.)	RANGE (MM.)	NUMBER INVERTED	NUMBER DIPHASIC
Lead I	988	+2.55	+2.80	+0.2 to +6.0	0	0
Lead II	989	+3.32	+2.80	−0.8 to +8.5	2	1
Lead III	974	+1.33	+1.50	−2.6 to +6.0	150	90

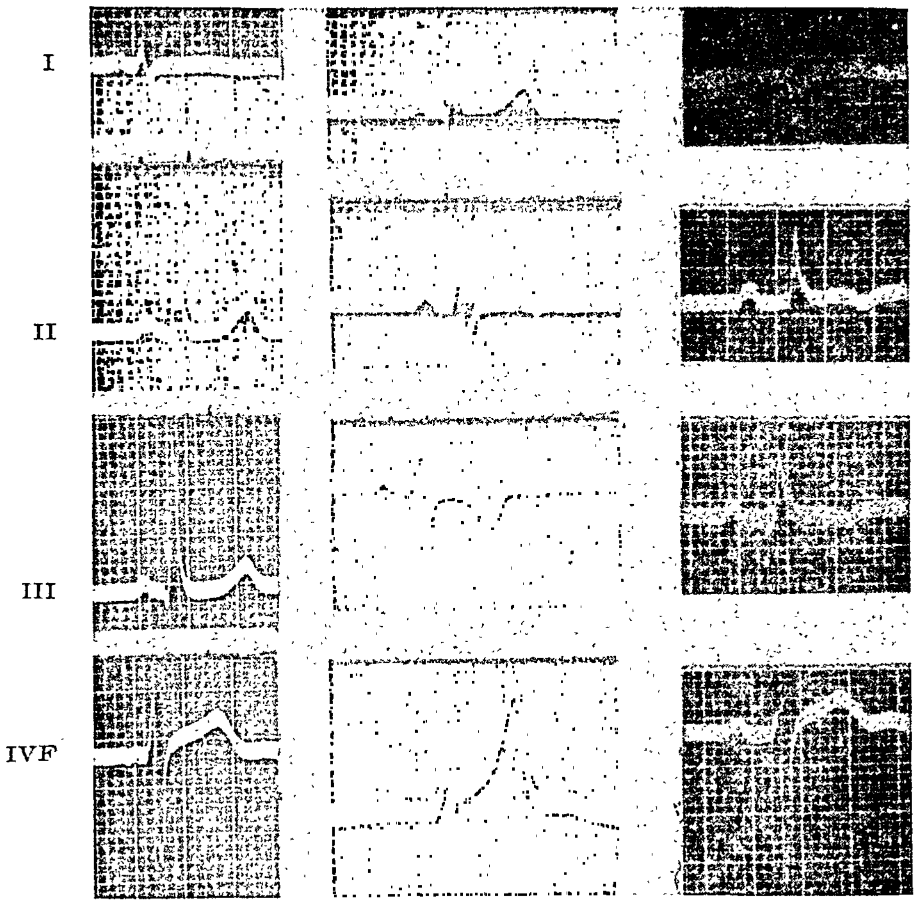


Fig. 13.—Low T_1. Fig. 14.—Inverted T_2T_3. Fig. 15.—Inverted T_2T_3.

These results emphasize the rarity of finding low or inverted T waves in Leads I and II in the electrocardiograms obtained from healthy persons of normal build, lying supine. Recently, considerable attention has been given[21, 22] to the exceptions to the rule that the T waves are normally upright in Leads I and II. These exceptions are important and deserve emphasis, but it must be remembered also that they occur infrequently and are usually due to some well-recognized cause, such as elevation of the left diaphragm, and the upright position.

THE Q-T INTERVAL

The Q-T interval was calculated according to the formula $Q\text{-}T = K \sqrt{\text{cycle length}}$. The range was from 0.30 to 0.59 and the mean 0.383.

THE U WAVE

The incidence of the U waves in the three standard leads and their direction and amplitude are shown in Table X. The fact that only two instances of inverted U waves were observed lends support to the generally accepted opinion that inversion is abnormal.

TABLE X

INCIDENCE AND AMPLITUDE OF U WAVES IN THE STANDARD LEADS

INCIDENCE OF U WAVES	
LEAD	NUMBER
1	268
2	448
3	141
1 and 2	131
1 and 3	14
2 and 3	66
1, 2, and 3	50
One Lead Only	284
No Leads	438

AMPLITUDE OF U WAVES				
	N	MEAN (MM.)	RANGE (MM.)	NUMBER INVERTED
Lead I	268	+0.12	+0.1 to +0.3	0
Lead II	448	+0.14	+0.1 to +1.0	0
Lead III	141	+0.13	+0.1 to +0.3	2

LEAD IVF

Lead IVF was obtained in all but six instances. The precordial electrode was placed on the chest at the outer border of the apex beat when this could be palpated, otherwise in the fifth intercostal space at the outer border of cardiac dullness. The left leg lead wire was attached to the precordial electrode and the left arm wire was attached to the electrode on the left leg.

The P Wave.—The P wave was visible in 967 of the 994 records. It was upright in 508 instances, ranging in amplitude from 0.1 to 1.5 mm., with a mean of 0.43. P was inverted in 126 instances and diphasic in 249. It was barely perceptible or small and bizarre in shape in 71 instances and absent in 40.

QRS Duration.—The duration of QRS ranged from 0.06 to 0.14 second, with a mean of 0.086. Although the range is the same and the mean value only 0.001 second smaller than for the maximum QRS duration in the limb leads, it does not follow that the values were the same in a given record. Frequently, the duration of QRS differed by 0.01 or 0.02 second in the limb and chest leads, but, on the average, it was not found to be longer in the chest leads as is sometimes stated.

The Q Wave.—In 795 records a Q wave was not seen; in 34 it was tiny and upright; in 45 it was represented by a slur at the base of the upstroke of R (fused Q); in 120 it was downwardly directed, ranging in value from −0.1 to −5.0 mm., with a mean of −0.83; Q was greater than

–1 mm. in 22 instances. Prominent Q was often associated with small S, tall R, and relatively great upward displacement of S-T, thus raising the suspicion that the precordial electrode was not properly placed over the cardiac apex.

The R Wave.—The R wave was always upright and ranged in amplitude from 1 to 29 mm. with a mean of 10.4. It was slurred in 82 instances and notched in 69. Thus, slurring and notching does not have the same significance as it does in Leads I and II where normally it is less commonly observed.

The S Wave.—This wave was absent in six instances, represented by a slur at the base of the downstroke of R in 11, and, in the remainder, varied from –0.2 to –28 mm. with a mean of –9.3. S was notched in 31 instances and slurred in 27.

The S-T Junction.—The S-T junction was displaced upward in 977 of the 994 records and in the remainder it was either downwardly displaced (three instances) or at the isoelectric level. The upward displacement varied from 0.1 to 5 mm. with a mean of 1.14. The extreme degree of displacement was associated with a small S wave (or no S) and may have been due to improper placing of the chest electrode.

The T Wave.—The T wave was upright in all but two instances, where it was diphasic; the range was from 1 to 15 mm., and the mean was 5.9. T was greater than 10 mm. in amplitude in 25 instances. Huge T waves have been shown[23] to be of pathologic significance in some cases. They are rarely observed in the electrocardiograms from healthy persons.

The U Wave.—The U wave was never found to be inverted and was present and upright in 915 of the 994 records. The range was from 0.1 to 1.2 mm., and the mean 0.24 mm.

LEAD IVR

Lead IVR was obtained in all but eleven cases. It was always taken immediately after Lead IVF was recorded, and the change in galvanometer connections was effected by simply turning the lead-selector switch. Thus, the two chest leads were taken under identical conditions.

The P Wave.—The P wave was always visible. It was upright in 976 instances and the value ranged from 0.1 to 2.3 mm. with a mean of 1.15. In the remaining 13 instances the P waves were inverted or diphasic.

The QRS Duration.—The duration of QRS varied from 0.06 to 0.14 second, and the mean was 0.087.

The Q Wave.—In 196 instances a downwardly directed Q was observed, which ranged in amplitude from 0.1 to 6.0 mm., with a mean of 0.80. In 38 of the 196, Q was more than 1 mm. Improper placing of the chest electrode was probably responsible for the extremely prominent Q waves. In 35 instances a tiny upright Q (R^1 new terminology) was

observed, and in 11 instances Q was represented by a slur at the base of the upstroke of R. In the remaining 747 records Q was not seen.

The R Wave.—The R wave was always upright and ranged in amplitude from 1.3 to 38 mm., with a mean of 17.8 mm.

The S Wave.—The S wave was downwardly directed in all but 23 instances, and the amplitude varied from −0.2 to −28 mm., with a mean of −8.34. Of the 23 remaining, 16 were fused, three were tiny but upright, and in four instances S was not seen.

S-T Junction.—The S-T junction was upwardly displaced in all but seven records; the range was from 0.6 to 4.5 mm. and the mean was 1.57 mm. In two records there was no displacement and in five there was slight downward displacement.

The T Wave.—The T waves were always upright and varied in amplitude from 2 to 22 mm., with a mean of 8.79.

The U Wave.—The U wave was present and upright in all but 20 records, where it was not seen. It varied in amplitude from 0.1 to 1 mm., with a mean of 0.28 mm.

COMPARISON OF LEADS IVF AND IVR

Some electrocardiographers have expressed a preference for the use of IVR rather than IVF. A comparison of the two, in so far as normal records are concerned, suggests that Lead IVF has one advantage; namely, that the amplitude of the several waves is smaller, which affords a more convenient normal range. In all other respects there seems to be no advantage either way.

DISCUSSION

The interpretation of an electrocardiogram ordinarily involves three distinct steps, namely, (1) the actual measurement of the various component parts, (2) the recognition of any deviations from the normal, and (3) a proper evaluation of the significance of the findings. The first step is essentially objective, if carried out in accordance with established procedure. The second step requires a thorough knowledge of the normal electrocardiographic patterns gained from past experience. The third step requires a full knowledge of the significance of the various deviations from the normal, together with a careful correlation with the other findings in the case. This part of the interpretation is largely subjective and reflects the judgment of the interpreter.

The need for information regarding the normal has led to an extensive study of the electrocardiograms obtained from healthy persons. Early studies* were carried out on only a small number of subjects, and the results did not disclose the full extent of the normal range. This, not infrequently, led the electrocardiographer wrongly to regard a par-

*See standard textbooks for references.

ticular measurement as abnormal and, as a consequence, to err in assessing its significance. More recent studies, including our own, involving large numbers of healthy subjects, have shown more completely the extremes of the normal range. The possibility that a few of the subjects in the present series had cardiac defects which could not be detected by ordinary methods of examination is freely admitted, but the number must have been very small. A follow-up study is, unfortunately, impossible at this time.

The results show that, even in a select group of young men, the electrocardiograms may vary within wide limits. The variations observed would undoubtedly have been greater if the subjects had included members of both sexes, with greater differences in body build, and if the subjects had been seated rather than lying when the records were obtained.

With regard to most of the electrocardiographic measurements, it is obvious that there is a considerable degree of overlap between the range of the normal and abnormal, and that there is no sharp dividing line between the two. This is responsible for one of the most important limitations of the usefulness of the electrocardiographic method. For certain electrocardiographic measurements it is necessary to know whether a given value falls clearly within the normal or abnormal range or in a middle or ambiguous range. If it falls in the ambiguous range, the probability that it is abnormal increases with progression from the normal to the abnormal. For example, in young adults, if the P-R interval is between 0.12 and 0.18 second, it is very likely to be normal; between 0.18 and 0.22 second it may be normal or abnormal, but the likelihood of its being abnormal becomes greater with each 0.01 second increase above 0.18. Serial electrocardiograms are helpful in that a definite change may indicate, in an individual case, the dividing line between the normal and abnormal even though both values lie within the so-called normal range.

It may not be out of place here to express an opinion regarding the usefulness of electrocardiography in aviation medicine. Failure of the circulation may be the limiting factor in man's adaptation to the sometimes exacting and abnormal influences of flying. Consequently, the physician responsible for the care of flyers will frequently be called upon to evaluate their cardiovascular status. In such an evaluation the electrocardiogram will often be helpful. This is true even when young, apparently healthy persons are concerned as shown by the findings in the present study. It becomes increasingly true as the flyers grow older and become subject to degenerative heart disease. The value of serial electrocardiography is also apparent, especially when the first tracings are taken when the subjects are young. Establishing a "normal" base line often aids in the interpretation of records

obtained at a later date. Naturally, the usefulness of this method in aviation medicine will vary greatly with the nature of the flying to be done.

SUMMARY AND CONCLUSIONS

1. The results of an analysis of the electrocardiographic findings in 1,000 young aviators have been presented.

2. The aviators represented a highly selected group of men between the ages of 20 and 30 years. None had any cardiac defect on physical and x-ray examination. The electrocardiograms (Leads I, II, III, IVF, and IVR) were taken with the subject recumbent and, with a few exceptions, in the basal state. The various measurements obtained from the tracings were recorded on master sheets and then analyzed statistically.

3. The results serve to emphasize the great individual variation in the electrocardiographic pattern and the wide range of normal values. These findings have been presented in detail with the aid of tables and charts.

4. Even after rejecting as frankly abnormal some of the extreme values observed, it is apparent that the "normal" extends well into what has commonly been regarded as the abnormal range. Some idea of the probability of a given value being abnormal is gained from the frequency with which it has been found to occur in normal persons.

5. The relatively large number of interesting and important electrocardiographic findings observed in young and apparently healthy aviators suggests that electrocardiography is of considerable value as an aid in the medical examination of pilots.

We wish to express our thanks to Dr. Paul D. White for his advice and critical review of the manuscript, and to Miss Helen M. Mitchell for her assistance in compiling the electrocardiographic data.

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SOME OBSERVATIONS ON THE CARDIOVASCULAR EXAMINATION FOR AIRCREW FITNESS

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WARTIME training of aircrew demands the largest number of well-trained personnel in the shortest time. Selection, therefore, becomes an important factor in eliminating wastage. Educational and aptitude tests have been combined with a strict medical examination in an effort to weed out the unfit and those whose chances of succeeding in operational flight are minimal for one reason or another. For preference, aircrew should be intelligent persons, medically fit, and endowed with skill, courage, and high spirits. As the strain of war reduces available man power, poorer types become applicants for the great fight. Some are highly motivated but have a poor constitution; others are driven by circumstances, the Army Draft, or by the derision and criticism of their neighbours. It is essential that considerable judgment be used so that valuable material be not lost by too strict adherence to meticulous medical standards.

In this war, experience has taught us that "Nature rather than nurture" seems to produce both the apt and the inapt pupil flyer. The cardiovascular system in relation to aircrew fitness surely reflects the gifts of Nature, and its reactions to the physical circumstances of flight have been much studied. Some observations on the normal variations in heart shape, heart sounds, heart action, and the place of the electrocardiogram and neurovascular instability in relation to the examination for aircrew fitness are presented in this paper. A more complete review is not attempted.

Heart Shape.—One can obtain by physical examination a fair appreciation of the position and size of the heart in the age group of potential aircrew (18 to 35 years). Routine 2 meter roentgen films of the chest are available to supplement the clinical observations. For proper interpretation of the film it should be appreciated that the shape of a normal heart is not limited to the classical forms of many texts. The normal frontal heart shadow varies in appearance over a wide range from long and narrow to being broad and transversely placed; the normal lateral or oblique views also vary considerably from deep to relatively shallow: a prominent pulmonary artery or a straight-line left cardiac border may be present in a normal person (1) with a long thin chest, or if the heart is (2) rotated anticlockwise on its long axis, or (3) displaced by slight scoliosis or sternal depression. In all such

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cases, however, careful search for the diastolic rumble of mitral stenosis at the apex, or other pathologic causes of increase in the left middle arc, should be made. Inaccurate alignment of the tube, subject, and film creates a shadow which is really a view slightly oblique to one side or the other of the straight P-A film. A routine check of each chest film for proper centering before interpretation is therefore strongly recommended.

Radiologists with experience in examining large numbers of recruits with supposedly normal hearts do not favor fixed standards for normal heart size. Measurements, nevertheless, are a valuable yardstick in the diagnosis of cardiac enlargement. The transverse diameter, the area of the frontal heart shadow, and the cardiothoracic ratio are those most frequently used. Where only one examination of the heart may be made, the frontal cardiac area is the most sensitive index of heart size. For repeated examinations on the same heart Comeau and White[1] have pointed out the simplicity and precision of the transverse diameter measurement in preference to the others. Standards based on weight and height have been established for the transverse diameter, Hodges and Eyster[3] for orthodiagraphy, and Ungerleider and Clark[7] for the teleoroentgenogram. A nomogram chart prepared by Ungerleider and Gubner[8a] permits the frontal area to be read directly from the long and broad cardiac diameters. Values exceeding 10 per cent above the predicted reading, from weight and height for the frontal area and transverse diameter, are usually abnormal.

Among the candidates for aircrew, an athlete of some experience may present roentgenologic evidence of slight cardiac enlargement according to accepted standards. In a recent article, Wilce[11] suggests that the intangible factors frequently found in true athletes, such as superior volitional trends and superior competitive spirit, may far outweigh the theoretical consideration of a relative anoxia in an hypertrophied heart at high altitudes. The modern use of oxygen above 10,000 feet definitely supports his inference that such cases might well be accepted for aircrew training. In the absence of etiological evidence of heart disease, and with normal physical findings, electrocardiogram, and exercise tolerance, it is suggested that values up to +15 per cent increase in the frontal area may be accepted for aircrew.

Heart Sounds.—Any attempt to judge the efficiency of the heart from the intensity of its sounds is fallacious. In healthy young airmen the variation in normal heart sounds is considerable. Detection of the minor differences depends to some extent upon the training and attention of the examiner. An impure quality or actual reduplication of the first heart sound at the apex or reduplication without accentuation of the second sound over the pulmonary area are not infrequent; change of posture or respiratory phase often corrects the sound to a normal single quality. A low third heart sound may normally be pres-

ent at the apex in thin persons, especially in the recumbent or left lateral position. Midsystolic clicks or sounds are ordinarily inconsequential.

Rarely, the low-pitched sound of auricular contraction may be heard before the first heart sound. This sound is not normally audible. Prolongation of auriculoventricular conduction time or complete heart block are the commonest causes. If an unstable auriculoventricular conduction time is present where the P-R interval varies with change in posture,[5] careful auscultation may elicit audible auricular contraction.

The first heart sound is frequently of low intensity when the P-R interval is at the upper limit of normal or slightly prolonged. This clinical finding has been confirmed repeatedly. One explanation is based on the theory that closure of the auriculoventricular valves contributes the significant energy in producing the first heart sound.[4] When auriculoventricular conduction is prolonged, ventricular filling has nearly been completed, and the valve cusps have already floated into apposition when isometric ventricular contraction begins. The auriculoventricular valves do not then close as vigorously as they ordinarily do. Proponents of muscular contraction of the ventricles as the primary basis of the first heart sound suggest that ventricular filling is already above normal when isometric contraction begins, and the pressure gradient within the ventricle is not increased as rapidly as usual. The vigor of the muscular contraction according to the latter theorists is a measure of the sound it is claimed to produce.

The presence of a systolic murmur in a candidate for aircrew calls for careful interpretation. Systolic murmurs in normal persons occur more frequently than is commonly recognized. In a study of 100 airmen free from heart disease, examined personally, four-fifths showed on a stethogram a systolic murmur of some kind when recumbent; pulmonic murmurs were slightly favored. The murmurs were loudest during expiration and in the supine position; they disappeared during inspiration and in most cases disappeared or were diminished on assuming the erect position.

In aircrew, systolic murmurs which vary with change in posture and disappear during some phase of the respiratory cycle, usually in inspiration, may be disregarded. Recognition of the etiological cause underlying a murmur is so much more important than the mere physical dynamics creating it. In this regard, the classification of cardiac murmurs into physiologic and pathologic types[10] is considered superior to the traditional terms "functional" and "organic." Venous hums originating in, or transmitted into, the innominate veins are also physiologic variations. If maximal to the left of the sternum below the sternoclavicular junction, they may be mistaken for the continuous "machinery" murmur of patent ductus arteriosus. Digital pressure on the internal jugular vein causes a venous hum to disappear. A loud systolic murmur and occasionally a thrill is sometimes heard below the lateral half of the clavicle and is due to compression of the corre-

sponding subclavian artery as it passes over the first rib. Cardiopulmonary systolic murmurs caused by compression of aerated lung substance during movement of the heart are unimportant except in their recognition and differentiation from pathologic murmurs. An increased rate of blood flow or anemia may cause a systolic murmur secondarily.

When a systolic murmur persists during all the common maneuvers in physical diagnosis, it is the result of some pathologic cause, such as rheumatic endocarditis, congenital anomaly, or dilatation of the valve ring. Candidates with recognized heart disease are unfit for service. If a slight but persistent murmur is the only finding and a negative or doubtful etiological history is obtained, the question of fitness for aircrew duties arises. Some argue that since the physical duties of an aviator are much less strenuous than those of the foot soldier, he may be accepted. The chance of recurrent rheumatic fever, the commonest etiological cause, or the possibility of subacute bacterial endocarditis make such a person a greater hazard in military service than one of sound health. Nevertheless, it is felt that medical standards could be judiciously relaxed in such cases and render valuable material available for aircrew.

Murmurs are an important diagnostic clue in congenital heart disease. The cyanotic forms of congenital heart disease are not acceptable for service. In principle, the acyanotic types should be rejected if recognized. History, physical examination, an electrocardiogram, and a roentgen chest film may each contribute information which will help in establishing the diagnosis. Many slight cases are missed even by experienced observers.

Heart Action and Function.—Meticulous adherence to fixed standards of pulse rate and blood pressure when assessing fitness for aircrew can also cause the loss of valuable personnel. The candidate, a volunteer for aircrew duties, is influenced by various emotional factors when he appears before the examining physician. Reassurance, rest in a quiet room, and, if necessary, re-examination on another day are strongly recommended if the readings are above the accepted standards. Aircrew standards have been adopted which allow considerable latitude. Pulse rates over 84 per minute are carefully investigated, and rarely is a person accepted with a persistent rate of 100 per minute or higher. The highest acceptable blood pressure is 145/95. At the lower range, pulse rates below 50 per minute and blood pressures below 100/60 are investigated. If asymptomatic and otherwise normal, persons with these and even slightly lower readings are acceptable. Some persons are unusually sensitive to the physician's presence and do not relax easily. In such cases a reliable technical assistant may find the pulse and blood pressure within normal limits when they were persistently elevated during repeated examinations by the physician. The wide range of normal pulse rate at rest or relative rest, in White's personal experience, ranges from 38 to 118 per minute.[9]

Table I shows some personal observations on 120 healthy young men. The mean systolic blood pressure was significantly lower when the emotional factor of the medical test was removed.

TABLE I.

	AT TIME OF ROUTINE MEDICAL EXAMINATION	TWO HOURS LATER WHEN EMOTIONAL FACTOR OF EXAMINATION WAS REMOVED
Pulse rate	75.44	75.90
Standard deviation	±8.24	±8.90
Systolic blood pressure	123.99	113.70
Standard deviation	±11.50	±10.48
Diastolic blood pressure	76.59	76.33
Standard deviation	±8.70	±7.98

The individual whose blood pressure descends with difficulty to 145/95 may be a potential hypertensive. This fact does not necessarily affect his ability to fly, and such persons often make good pilots. Persons with a blood pressure of 100/60, without symptoms and with a good exercise tolerance, are acceptable. A history of postural vertigo and frequent fainting attacks entails rejection, more especially if postural hypotension is recognized in addition.

Exercise tolerance tests in some form have long been used as a measure of cardiovascular efficiency and physical fitness. It has been demonstrated to our satisfaction that no one of these tests uniformly measures the physical fitness of the individual and they are at best an uncertain index of cardiovascular efficiency.

For twenty-five years in the examination for aircrew, the candidate has been requested to maintain a column of mercury 40 mm. in height by respiratory compression as long as he can, and the pulse rate has been noted in five-second intervals. Considerable importance was originally attached to the nature of the pulse-rate curve, a low level sustained through 60 seconds being the best type. From correlation studies it is now known that the type of curve is not an effective selector of potential aircrew; the test is still used but interpreted as one of endurance, stamina, and spirit, "when the going gets difficult." In this regard 55 seconds is considered a critical level.

Variations in Rhythm.—Sinus tachycardia (rate above 100) should be evaluated as accurately as possible. Nervousness or excitement is responsible for most cases, but infection, fever, fatigue, and mild hyperthyroidism should not be overlooked. When it forms part of a mild autonomic instability, statistics show that the candidate stands an average chance of finishing his course but is usually considered inferior combat material. Further reference is made to this subject later.

Sinus bradycardia (rate below 55) is not uncommon. A history of recent infection, such as influenza, may be elicited. All doubtful cases should have an electrocardiogram as part of their investigation.

Sinus arrhythmia is very common and may be disregarded in the young applicants for aircrew. If marked and associated with occasional premature beats, the resulting arrhythmia may be difficult to distinguish by clinical examination. An electrocardiogram is recommended in such cases.

In general, the candidate with a history of paroxysmal tachycardia with symptoms should not be in aircrew. This is commensurate with the importance of his post and the strain of his duties. Unless incapacitated by frequent attacks, he can be profitably employed in a noncombatant position on the ground. If the trained pilot complains of symptoms due to palpitation or of a paroxysm of tachycardia, he may be using a lever to avoid operational duty or he may simply be worried about his ability to continue flying. General principles are applicable in the latter case; if he has incapacitating symptoms during the attack, no matter how short, he should not hold a position which would endanger the lives of his crew or the loss of an aircraft. A few well-chosen questions may elucidate an underlying psychological situation in the former instance.

The commonest arrhythmias seen in potential aircrew are due to premature systoles. It is frequently possible to distinguish them by clinical examination, but an electrocardiogram is recommended if they are frequent. Occasional supraventricular or ventricular premature contractions may be disregarded. If occurring with moderate frequency, an attempt should be made to find the cause and to remove it if possible. Any candidate with electrocardiographic confirmation of (a) short runs of premature beats, (b) multiple foci of premature auricular or ventricular contractions, (c) premature beats with a heart rate above 110 per minute, (d) increase in the number of premature beats after exercise, and (e) inversion of the T wave in the postextrasystolic contraction in the electrocardiogram[8b] should be rejected. Abnormal ectopic rhythms are not acceptable for military service.

Electrocardiography.—The place of electrocardiography in aircrew selection is not easy to evaluate accurately. In a routine series of apparently healthy aircrew candidates, only 0.45 per cent of definitely abnormal tracings were found.[2] Although considerable economy is realized in early rejection of even such a few persons, it would scarcely seem justifiable to record electrocardiograms routinely on all potential aircrew. Electrocardiography does serve a very useful purpose, however, in selected cases in young persons and is recommended as a routine part of the examination of all aircrew personnel over 35 years of age.

Some interesting variations have been recorded in routine series of electrocardiograms. They include the "short P-R, wide QRS" picture first described by Wolff, Parkinson, and White,[12] sinus bradycardia at a rate of 38 per minute and alteration in the auriculoventricular

conduction time with change in posture,[5] the P-R interval being prolonged when in the recumbent or head-down position.

For selection purposes, if the electrocardiogram indicates myocardial damage or impairment of the conducting tissues, the candidate should be rejected. Complete heart block or bundle branch block (QRS, 0.12 second or longer) is cause for rejection. An asymptomatic short P-R, wide QRS syndrome does not entail rejection. Persistent prolongation of the P-R interval up to 0.28 second is occasionally found in normal healthy persons. It does not appear to be any particular hazard in the air, yet one hesitates to accept such a candidate. Under present standards they are unfit for aircrew. Cases are known of aviators continuing a successful and uneventful career with prolongation of the P-R interval to 0.25-0.27 second without symptoms or knowledge of their condition (Graybiel). Valuable personnel may thus be unnecessarily wasted if every case with a prolonged P-R interval is rejected from aircrew.

Left or right axis deviation should not entail rejection per se. Further investigation is indicated. Neither should slight elevation or depression of the S-T segments alone cause rejection. The whole electrocardiographic picture must be considered in relation to the history and the clinical findings.

T-wave inversion in Lead III is usually benign. Coronary heart disease is rare among aircrew candidates; consequently, if T-wave inversion is present in the other limb leads or in the chest lead, other causes must also be considered. Usually enough supporting evidence, either historical, clinical, the x-ray, or the electrocardiogram itself, can be found to substantiate a diagnosis. The subject of such T-wave inversion is usually unfit for aircrew.

The origin and type of premature beats are readily recognized in an electrocardiogram. As stated previously, premature beats occurring in runs, or arising from multiple foci, occurring at a heart rate above 110 per minute or increasing in number after exercise, entail rejection. If the T wave of the postextrasystolic contraction is inverted, organic heart disease is frequently present;[6b] such a candidate is unfit. Ectopic rhythms such as auricular flutter, which with 4: 1 block may easily simulate normal rhythm, and auricular fibrillation are unfit for aircrew. Nodal rhythm is better rejected.

In the early recognition of silent coronary heart disease during the third and fourth decades, routine electrocardiograms on aircrew personnel are an important diagnostic aid. Once definite evidence of myocardial impairment or conduction tissue defect is discovered, the subject should be grounded.

Neurovascular Instability.—Under the prevailing system of volunteer enlistment, most cases with labile pulses and blood pressures are due to nervous excitement lest they may not "make aircrew," the goal of their ambition. Many otherwise acceptable subjects have been rejected and, perhaps, still are being rejected because, with unstable

pulse and blood pressure readings, they have been unable to pass fixed numerical standards. Minor degrees of autonomic imbalance manifest in increased vasomotor and sudomotor activity are not associated with an increased "washout" rate in pilot training.

Marked autonomic imbalance calls for careful assessment of the candidate's temperament and emotional stability. An emotionally unstable person may learn to fly but does not make good combat aircrew material. Under the physical and psychic strain of war he is likely to break down. Borderline cases are frequent, and skilled psychiatric opinion is advised before they are accepted.

The syndrome called neurocirculatory asthenia has not been a problem in aircrew training in Canada. Several factors are responsible.

a. Rejection at recruiting level of any person with a history of the symptom complex.

b. Absence of strenuous physical exercise comparable to infantry training. (Routine gymnastics and athletics for "physical fitness" form part of aircrew training.)

c. Volunteer service automatically selects those with good motivation.

d. Careful appraisal of any case with vasomotor or autonomic instability before acceptance for training.

The descriptive term neurocirculatory asthenia for the well-known syndrome complex is used reservedly. If an accurate evaluation of the mixed symptomatology were made in each case, the diagnosis of anxiety state with cardiac neurosis or psychoneurosis with cardiovascular manifestations would be more frequently applied. The constitutionally inferior person, the long and lean individual with poor posture, flabby muscles, and pronounced vasomotor instability, in whom the psychic factor is probably the most amenable to treatment, is another type in whom the characteristic picture may be found. Others, however, with a stronger natural constitution, may break down under physical or nervous strain when they have been devitalized by infection, fatigue, or anxiety. Michael, writing on the aftermath of Pearl Harbor, compares men's minds to ships which sink when their buoyancy is destroyed.[6] The prognosis for the group better endowed by Nature is hopeful, for the cause can be remedied.

Fear and anxiety neurosis, hysteria, and reactive depression occur during training or under the strain of operational flights and are sometimes referred to the cardiologist because of cardiovascular symptoms. The latter may be prominent but are inconsequential. Treatment should be directed at the basic disturbance.

COMMENT

In aircrew selection, the cardiovascular examination naturally holds a prominent place. Perplexing problems arise in assessing the fitness for aircrew of borderline cases. The wide range of normal values is becoming better known and, with this, some "problems" have disappeared. Still, loss of valuable material results from too meticulous

adherence to fixed standards; some suggestions are made in this paper where judicious relaxation of standards might be made. The utilization of all desirable personnel becomes more important as the drain of war on man power continues. To some extent, the fortunes of war influence the demand for men and this secondarily affects the medical restrictions imposed on applicants for training. Poorer physical and constitutional types will become more frequent candidates. A serious attempt should persistently be made to exclude those persons with a definite neuropathic predisposition and the individuals poorly endowed by Nature referred to above. They rarely make satisfactory service personnel and never good combat aircrew, which, after all, is essentially what medical selection for aircrew fitness sets out to provide.

SUMMARY

1. Within the cardiovascular examination itself there are many perplexing problems in relation to selection and fitness for aircrew.

2. Normal cardiovascular function in a stable person without historical or clinical evidence of heart disease was the standard originally set for entry for aircrew training. The strain of war demands modification of the standards originally imposed.

3. Personal observations are made on the frequency of normal variations in heart size, shape, and action found in routine examinations on aircrew personnel. Some suggestions are made where relaxation of strict standards could make otherwise acceptable persons eligible for training, without undue hazard to themselves or to the Service. The place of electrocardiography and neurovascular instability in aircrew selection is briefly discussed.

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CARDIOVASCULAR EXPERIENCES IN AN ARMY GENERAL HOSPITAL

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THIS report is a review of the cases of cardiovascular disease seen in an Army general hospital. To such a hospital gravitate the problem cases, the unusual conditions, cases requiring prolonged or special treatment, and other cases for further observation and disposition. Since cardiovascular diseases, by and large, fall into one or another of these categories, it is logical that a large percentage of these cases turning up in the Army eventually find their way to a general hospital. A review of such cases should be of interest in showing not only the types of cases encountered but also the problem of cardiovascular diseases in the Army.

The material for this review consists of the cases admitted to the Lovell General Hospital, Fort Devens, Massachusetts, which is the Army general hospital serving the military installations in the New England states, upper New York state, and certain overseas bases. This hospital has been in operation for a little over two years and during this time has had approximately 10,000 admissions. Of this number, there were 440 cases of "organic" cardiovascular diseases and about an equal number of "functional" cardiovascular disorders. We have no information concerning the Army population from which these cases were drawn and hence can give no percentage incidence of these conditions in the Army. Further, it should be mentioned that, during the period covered by this report, the vast majority of the admissions to the hospital represented casualties of mobilization and training, few, if any, being related to actual combat.

Except for a few pertinent observations, no detailed analysis of all of the data is presented, as such a presentation would be beyond the scope of this paper, which is primarily a general survey of the problem. With this in mind, the various types of diseases will be taken up and brief mention made of any salient features.

ORGANIC CARDIOVASCULAR DISEASES

The cases of "organic" cardiovascular diseases are classified etiologically in Table I.

Rheumatic Fever (59 Cases).—These cases were observed either during the active phase of the disease or during convalescent care following the acute illness elsewhere. It was possible to give these patients the optimum of care because the duration and type of hospitalization was determined solely by the activity of the disease without concern for the financial or economic status of the patient. Twenty-five per cent

TABLE I

ORGANIC CARDIOVASCULAR DISEASES

Rheumatic fever	59
Rheumatic heart disease	90
Hypertension	88
Arteriosclerosis	109
Cardiovascular syphilis	3
Congenital heart disease	7
Dysfunction of rhythm or conduction	34
Miscellaneous cardiac diseases	15
Miscellaneous vascular diseases	35

of the cases showed evidences of residual valve deformities at the end of their illness, but it is quite possible that some of these cases had valvular lesions prior to the current attack of rheumatic fever. The disposition of these cases varied with the individual case. Many of them were placed on limited service for three to six months and then returned to full duty. Others were discharged from the Service, particularly if they gave a history of frequent attacks of rheumatic fever or had residual valvular damage. A few in this latter group were retained on limited service if they were particularly valuable in their jobs. In recent months limited service duty has been for the most part abolished, so that now we are discharging almost all of these men, retaining only a few who can be rehabilitated to full service within a short while.

Rheumatic Heart Disease (90 Cases).—These cases had been discovered during routine examinations or hospitalization after entrance into the Army. None of them had had any acute illness in the Army, which could be considered rheumatic fever in any form. In our opinion, all of these lesions were present prior to Army service and were unrecognized at the time of entrance examination: hence, they can be placed in the class of "preventable" cardiac casualties. However, they represent less than 1 per cent of the total hospital admissions, so it is a relatively small group in the total number of casualties. Under the conditions existing in many induction stations, it is not surprising that some lesions are overlooked and are subsequently discovered only during the leisure and quiet of a hospital or clinic. We feel that the "screening out" of valvular heart disease has been well accomplished during the present mobilization. Of particular interest in this group of patients were the observations that 40 per cent of the cases had no symptoms of heart disease, even during active military service, and that 60 per cent of the cases were discovered incidentally during routine examinations or while hospitalized for some other condition. Three cases had superimposed subacute bacterial endocarditis. Practically all of the cases in this group were disposed of by discharge from the Service.

Hypertension (88 Cases).—The evaluation of abnormal elevations of the blood pressure has presented quite a problem, not only in the rela-

tive number of cases involved, but also in regard to disposition. The Army has specific standards of blood pressure values, but the difficulties arise in judging the significance of any particular blood pressure determination. This may vary considerably in the same person, depending upon the circumstances of the examination, so it is largely a matter of opinion as to just which patients should be considered as having hypertension. Many individuals will show abnormal elevation of the blood pressure on initial examinations, but, subsequently, will have normal pressures following varying periods of normal activity, restricted activity, or complete bed rest. However, the more restriction required to produce lowering of the pressure to normal, the more abnormal becomes the individual's existence, under which circumstances the blood pressure values are of questionable significance. Since an arbitrary line must be drawn somewhere, it has been our policy to have those patients under observation for hypertension on an ambulatory status but resting in bed for one-half hour prior to determination of the blood pressure three times daily. If, under these circumstances, a patient had a persistent blood pressure above 150/90, he was considered to have hypertension. Those patients who had nonpersistent elevations of the blood pressure were classified as "vasomotor disturbance with tendency to hypertension," a group that will be taken up later under functional cardiovascular diseases. Of the 88 cases of hypertension, 19 patients had varying degrees of cardiac enlargement and were considered to have hypertensive heart disease. Most of these were mild to moderate in degree, with only a few in the stage of frank congestive heart failure. Four of the cases of hypertension were associated with chronic nephritis, one was associated with polycystic kidneys, and four were of the "malignant" variety. One of these latter cases came to post-mortem examination and was found to be on the basis of healed periarteritis nodosa, particularly marked in the kidneys.

Arteriosclerosis.—As might be anticipated, this condition was found, for the most part, in the older age group of commissioned and noncommissioned officers. It occurred as a primary diagnosis in 109 cases, 47 of which were considered to have generalized arteriosclerosis uncomplicated by heart disease. Some in this latter group presented symptoms referable specifically to the cerebral or peripheral circulation and others showed evidences of generalized deterioration, but, for the most part, the arteriosclerosis was not out of proportion to the patients' ages and was not incapacitating to any significant degree. There were 18 cases classified as having arteriosclerotic heart disease, as manifested by symptoms of cardiac disease (exclusive of chest pain) out of proportion to their ages. Twenty cases were considered to have true angina pectoris. One of these was of particular interest because he was only 24 years of age, gave a classical history of the disease, and had other findings consistent with hypercholesteremia. There were 24 cases of coronary occlusion with myocardial infarction, as evidenced by

classical histories and characteristic electrocardiographic findings. Three of these cases are noteworthy because their ages were 21, 24, and 30 years, respectively. The disposition of all of these cases was largely an individual problem. If the condition was considered to be service-connected and if the individual was particularly valuable in a specific sedentary position, he was retained in the Service. Otherwise, they were separated from the Service.

Cardiovascular Syphilis.—This was a relatively rare condition, occurring in only three cases. Two of these had simple, uncomplicated aortitis, and the third had aortic insufficiency with cardiac enlargement. The decrease in cardiovascular syphilis in general, due to more adequate treatment and the routine induction serology which identifies and separates the syphilitic person, probably explains to a large extent the relatively infrequent occurrence of this condition in the Army.

Congenital Heart Disease (7 Cases).—There were two cases of coarctation of the aorta, two cases of complete dextrocardia, and one each of patent ductus arteriosus, interventricular septal defect, and bicuspid aortic valve. The latter case had superimposed subacute bacterial endocarditis.

Dysfunctions of Rhythm or Conduction (34 Cases).—These occurred as incidental and isolated electrocardiographic findings in patients with otherwise normal hearts. There were thirteen cases having varying degrees of auriculoventricular or intraventricular block, two of the latter belonging to the so-called "Wolfe, Parkinson, White syndrome." Twelve cases had arrhythmias due to either auricular or ventricular premature beats. There were six cases of idiopathic auricular fibrillation, two cases of paroxysmal tachycardia, and one case of auricular flutter.

Miscellaneous Cardiac Diseases (15 Cases).—There were six cases of isolated pericarditis; two were purulent in type, two were tuberculous in origin, and two were of the so-called "idiopathic" variety. Cardiac enlargement of undetermined etiology was found in five cases, all of which showed significant enlargement of the heart on physical examination and by x-ray studies in young adults without hypertension and without other evidences of cardiovascular disease. There were three cases of traumatic heart disease, two involving foreign bodies in the heart, and one of myocardial contusion. There was one case of acute bacterial endocarditis secondary to a lobar pneumonia.

Miscellaneous Vascular Lesions (35 Cases).—There were twelve cases showing peculiar vasospastic changes in the fingers, which we placed in the category of Raynaud's phenomena. It occurred in individuals who previously had had no difficulty until they were stationed in cold climates. The involvement varied from a portion of one or two fingers to the entire hands, and the disturbance tended to subside on return to a more temperature climate. While the involvement varied between individuals, it was quite constant for each patient and could be reproduced by immersing the hands in ice-cold water. There were eleven cases of

venous thrombosis, ten of them in the nature of thrombophlebitis and one of them traumatic in origin. Five cases had so-called "causalgia" and three cases had thromboangiitis obliterans. There were four cases of arteriovenous fistula, two congenital, and two traumatic in etiology.

FUNCTIONAL CARDIOVASCULAR DISORDERS

Some mention should be made of the large group of cases classified as "functional" cardiovascular disorders. It consists of those individuals who were hospitalized or came under the observation of the cardiovascular consultants because of symptoms or signs suggestive of cardiovascular disease. In many cases, the symptoms were of sufficient degree to incapacitate the individual. After thorough studies, all were found to have no evidences of organic cardiovascular disease nor any disturbances in cardiac rhythm or conduction. The exact number of these cases is not tabulated, but their number approached that of the cases of "organic" heart disease. They presented a tremendous problem in diagnosis and disposition. Time does not permit an adequate presentation of this problem, however, and our data on it are not completed, so only a few salient points will be given.

Neurocirculatory Asthenia—Psychoneurosis.—These two conditions, which represent the vast majority of the functional disorders, are grouped together because there is, as yet, no clear separation of the various conditions classified under one or the other of these designations. The question as to how much is psychogenic and how much is physiologic in the etiology of these conditions, is still the subject of numerous discussions and extensive investigations. In our experiences, most of the cases designated as neurocirculatory asthenia presented definite psychoneurotic traits, usually of the anxiety type. In only 31 cases did we make the diagnosis of "classical" neurocirculatory asthenia on the basis of the association of the symptoms exclusively with effort. Even some of these had certain psychoneurotic tendencies and the diagnosis was not without question. By far the greater number had symptoms at rest as well as on exertion, and they usually occurred in attacks during certain "settings." A few cases of cardiac neurosis were encountered which we considered distinct from both neurocirculatory asthenia and psychoneurosis of the anxiety type. Regardless of the specific designation of these cases, practically all of them were incapable of performing any useful service in the Army and, therefore, were separated from the Service. Efforts to rehabilitate these men met with uniform failure. A rare case with postinfectious type of neurocirculatory asthenia was restored to full duty after a conditioning period.

Vasomotor Disturbance With Tendency to Hypertension.—This group consisted of those patients, 81 in number, under observation for hypertension, who did not show a persistent elevation of the blood pressure above the normal limits. It is the class of individuals sometimes designated as "prehypertensive." In the usual case, the blood pressure was

found elevated to abnormal levels during a routine examination but subsequently returned to normal levels after varying periods of hospitalization. Few had symptoms usually associated with hypertension, but many of them presented various complaints, usually psychogenic in character. In the majority of these cases the neuropsychiatric consultant made a diagnosis of psychoneurosis, more commonly of the anxiety type. Most of these patients were incapacitated for any useful service because of psychogenic symptoms, but a few, however, were returned to limited service in positions where there were no particular stresses or strains.

There were a few patients without symptoms who were hospitalized because of cardiac murmurs considered to be of organic origin, but which we interpreted as functional in nature. These were returned to duty after being given reassurance as to their cardiac status. There was also a small group of patients who had symptoms suggestive of heart disease which were found to be on the basis of extracardiovascular conditions, such as obesity, pulmonary disease, etc.

COMMENT

An interesting variety of cardiovascular diseases is seen in an Army general hospital. They represent only a small portion of hospital admissions, but the problems involved in these cases are numerous and stimulating. Unfortunately, most of the cases are not amenable to restoration to full service duty and the cardiovascular consultant is more concerned with the evaluation and disposition of cases than he is with actual therapeusis. Nevertheless, this function of identifying and separating the potential cardiovascular casualties is a very important one to the Army.

CARDIAC PROBLEMS IN A STATION HOSPITAL

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THE distribution of cardiac problems in the Army is different from that in civil life in that young people are predominant in the Service, and the examination at induction centers eliminates, for the most part, the group with organic heart disease.

During the course of a twelve-month period, there were only thirty-six soldiers who were discharged from the Army at the Station Hospital, Fort Devens, Massachusetts, because of organic heart disease. Twenty-three had rheumatic valvular damage; seven, congenital defects; three, paroxysmal arrhythmias; one, syphilitic aortic regurgitation; one, subacute bacterial endocarditis, and one, angina pectoris. In view of the fact that all selectees in New England come to the reception center at Fort Devens, this small number emphasizes the excellence of the examination in reference to the heart done at the induction stations.

Coronary and Hypertensive Heart Disease.—As a result of dealing with young people, the problem of coronary and hypertensive disease plays a minimal role. Although no exact figures are available, it is an impression that the incidence of degenerative disease, even in the older age group, is less than in civil life. This, too, may be due to the selection of personnel. It is to be noted, however, that these diseases occasionally do occur in the young. We had one soldier 19 years of age who developed a coronary thrombosis with myocardial infarct, and subsequently showed congestive heart failure and died. Similar incidents have been reported from other army installations. It must be emphasized that apparent good health and youth should not preclude the consideration of the degenerative diseases in the presence of a clinical picture.

Acute Rheumatic Fever.—The clinical picture and course of acute rheumatic fever in the Army are no different from that generally described. One is impressed, however, by the large number of antecedent sore throats, and by the fact that more than 50 per cent of the patients present themselves in the first attack. Patients with rheumatic fever are a special problem for the Army, as to both their care and their disposition.

The soldier is kept in bed until all clinical signs of activity have ceased, and the sedimentation rate has reached, or approached, normal. Then there follows a period of supervised graduated activity until the patient is able to stay up all day and participate in mild exercises.

Those soldiers who are admitted in an acute attack and show evidence of residual damage at the end of their convalescence are discharged from

the Service. The Surgeon General has not established a policy which requires the discharge of men who have an attack of rheumatic fever in the Army because they have a history of attacks of rheumatic fever in civil life. I believe, however, that they are poor risks, despite the evidence that they are not likely to develop organic valvular damage with their recurrent attacks.[1, 2]

The group of soldiers who show no heart disease at the end of convalescence from their first attack are given a one-month sick furlough, and brought back to the hospital for further examination before return to duty. The Surgeon General in a recent directive has indicated that individuals may be retained in the Army who have apparently fully recovered, but they should not be considered as qualified for full military duty until a period of six months has elapsed.[3]

Inasmuch as the final evaluation of the state of the valves must be delayed for several years after an attack of rheumatic fever, an arbitrary period of observation is designated to eliminate the greatest number who are likely to develop organic valvular damage. The procedure outlined, no doubt, returns to duty some soldiers who will subsequently develop organic valvular damage. It is felt, however, that the health of the individual is not jeopardized since he will be subject to constant medical supervision. It has been pointed out previously that 50 per cent of patients showed no evidence of heart disease following acute rheumatic fever.[4] As follow-up studies are not available as yet on the group who were discharged to duty, it is not possible to state whether this continues to hold.

Neurocirculatory Asthenia.—Dyspnea, palpitation, easy fatigue, and precordial pain without organic basis is a symptom complex familiar to all. In a twelve-month period there were over 300 soldiers with the syndrome at this hospital (nearly ten times as many as those with organic heart disease). There are, of course, all gradations of severity, from the soldier who has symptoms at rest, to the one who can perform light duties, from the soldier who complains almost immediately on arriving at camp, to the one who manages to carry out part or all of his basic training.

One usually finds that the symptoms date back many years. In this group only two or three soldiers developed symptoms for the first time after being in the Army. Most of these men have somatic complaints elsewhere in the body, but the symptoms referable to the heart completely overshadow these. Although some of the soldiers claim that they do not know what ails them, the majority will relate that physicians had told them at one time that there was something the matter with their hearts.

The psychiatric approach to this problem reveals the fact that we are dealing with unstable individuals who make a poor adjustment to civilian life. Since it is felt that these patients are psychoneurotic and are obviously constitutionally inferior, I am in complete accord

with Dr. Paul D. White who feels that they should never be admitted to the Army even if the condition is mild.[5] The major problem for the psychiatrist at the induction centers is to recognize the men with conscious motivation.

An attempt was made to return mild cases to duty or to adjust their duties to their capabilities. For the most part, however, these soldiers exerted a demoralizing effect on any unit to which they were attached. They could not do calisthenics, hike, or do laborious work. They reported to Sick Call frequently. In this way they interfered in almost every training program. Moreover, when a group of soldiers recognized that one member was apparently excused from some duties, those symptoms resulting in the excuse became just as contagious as the exanthemas.

Soldiers with this condition should be separated from military service unless they have special training to perform a sedentary job, and can do it without symptoms. The loss in man power resulting from such a program will be more than compensated for by the quality of work of the remaining soldiers.

SUMMARY

The picture that I have given of cardiac problems at the Station Hospital at Fort Devens is probably the same for all hospitals serving troops young in their Army career or in noncombatant branches. As the training program becomes more severe, most cardiacs (organic or functional) fall by the wayside.

The situation could be called ideal if we had only cases of rheumatic fever and degenerative diseases to report. The presence of the large number of soldiers with neurocirculatory asthenia is a challenge to the examining physicians at induction stations.

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HEART DISEASES AND DISORDERS AS CAUSES FOR EVACUATION FROM THE SOUTH PACIFIC COMBAT AREA

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A RECENT report of 900,000 rejections for military service shows cardiovascular diseases as third in importance (96,000), being surpassed only by dental defects (188,000) and defective eyes (123,000) as causes for refusal of enlistment. The purpose of the present study was to determine the adequacy of this screening, as shown by the appearance of cardiovascular disease as a cause for evacuating military and naval personnel from the combat area of the Solomon Islands and adjacent waters. The basis for the analysis is the experience of the hospital ship, U.S.S. ————, in transporting sick and wounded from this area from July 1, 1942 to July 1, 1943, and the experience of a Naval Base Hospital in New Zealand from Sept. 8. 1942, to Sept. 13, 1943.

In this year, 9,085 new patients or single readmissions (Army, Navy, and Marines) were admitted to this hospital ship, while there were 13,000 total admissions to the Base Hospital.* The senior author was not at that time attached to the ship but to the shore hospital in New Zealand to which the U.S.S. ———— evacuated 993 of these patients. The records of the patients transported on the hospital ship have been consulted, and the information added from further observation on the ship has been critically reviewed by one of us (H.B.S.), from the standpoint of a cardiologist, while those in the Base Hospital have been analyzed by the other (S.M.).

As would be expected, a certain number of men who had become incapacitated, and in whom the cardiovascular system was erroneously incriminated, were evacuated from the forward areas without opportunity for adequate study, and the attempt has been made to analyze the data to arrive at the correct diagnosis. Such an attempt is not without danger of inaccuracy but it is believed that the results are approximately correct.

HOSPITAL SHIP EXPERIENCE

The original admission diagnoses to the ship are shown in Table I.

It is obvious that even if all of these patients had been suffering from cardiovascular disease, the percentage evacuated from this cause is very small; but the observations made while the patients were aboard the hos-

The opinions or assertions contained in this article are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

*This figure from the Base Hospital is the total number of admissions and includes readmissions in each instance as if new patients. The actual number of individuals would be somewhat lower; this figure is not available at the moment.

TABLE I

VALVULAR DISEASE	DIAGNOSIS UNDETERMINED	NO.
Valvular heart disease	1	11
Myocarditis, rheumatic	1	1
Carditis, rheumatic	2	2
Endocarditis, acute		2
Endocarditis, chronic		1
Subacute bacterial endocarditis		1
		18
DEGENERATIVE HEART DISEASE		
Hypertension	1	20
Myocarditis, chronic	2	9
Angina pectoris	3	11
Thrombosis, coronary artery	2	7
Arteriosclerotic heart disease	1	1
Coronary heart disease		2
Arteriosclerosis, coronary		1
Cardiac asthma		1
		52
MISCELLANEOUS		
Effort syndrome	2	14
Tachycardia	2	12
Cardiac arrhythmia	1	4
Cardiac neurosis		2
Hypotension		1
		33
Total cardiovascular cases*		103
Percentage of total cases admitted		1.13

*The records of two other patients were not available. They are not included in the series.

pital ship resulted in modifications of these diagnosis as shown in Table II. Such changes in diagnosis could not always be made prior to evacuation from the ship to a shore base hospital, due to the short time the patients were aboard, and they represent the personal opinion of the senior author.

It is concluded that the reasonably well-proved incidence of cardiovascular defects causing admission to this hospital ship from the combat area of the Solomon Islands, and as far south as New Caledonia, is 0.6 per cent.

NAVAL BASE HOSPITAL EXPERIENCE

At U. S. Naval Base Hospital ———, in New Zealand (originally designated U. S. N. Mobile Hospital), patients were received from various hospital ships, transports, occasional combat ships, local marine and naval establishments, and from another base hospital in this country. Two important modifying factors are present: one is the higher incidence of recurrent malaria with readmissions from local marine establishments, and the other is the longer period of observation which was possible in the hospital as contrasted with the few days aboard the hos-

TABLE II

VALVULAR HEART DISEASE	CHANGES IN DIAGNOSIS	PROVED CASES
Valvular heart disease of all types but presumably of rheumatic origin. In no case were the findings typical. The heart was negative by x-ray in 3, and no x-ray was made in 1)		4
Other conditions originally diagnosed chronic endocarditis or valvular disease:		
Chronic bronchitis	1	
Bronchiectasis (?)	1	
Myalgia of chest wall	2	
Recurrent malaria	1	
Effort syndrome	1	
No cause for diagnosis discovered but no evidence of heart disease	3	
	9	
Acute endocarditis (proved by autopsy)		1
Acute endocarditis disproved	1	
Subacute bacterial endocarditis disproved	1	
DEGENERATIVE CARDIOVASCULAR DISEASE		
Arterial hypertension		6
Other conditions originally diagnosed hypertension:		
Fatigue	2	
Anxiety neurosis	3	
Recurrent malaria	1	
Arthritis of spine	1	
Chronic nephritis	1	
No hypertension or other disease	2	
	10	
Coronary heart disease		5
Arteriosclerotic heart disease		1
Arteriosclerotic heart disease originally diagnosed but no confirmatory evidence. Symptoms considered due to heat exhaustion and salt loss	1	
Coronary thrombosis		4
Angina pectoris		7
Angina pectoris originally diagnosed but not characteristic and symptoms considered due to:		
Anxiety neurosis	3	
Neurocirculatory asthenia	1	
Probable arthritis of spine	1	
Malaria	1	
	6	
Cardiac asthma—negative heart examination and considered allergic in type	1	
Myocarditis—in only one instance was the diagnosis of heart disease confirmed and the proper diagnosis of coronary heart disease, arteriosclerotic, is preferable		1
Other conditions originally diagnosed myocarditis were:		
Varicose veins and extrasystoles	1	
Varicose veins and respiratory infection	1	
Obesity	2	
Malaria	1	
Vague chest pain of atypical nature	2	
Auricular fibrillation from severe combat injury to chest	1	
	8	

TABLE II—CONT'D

FUNCTIONAL CARDIAC DISORDERS	CHANGES IN DIAGNOSIS	PROVED CASES
Effort syndrome or neurocirculatory asthenia		13
Other conditions originally diagnosed effort syndrome:		
Fatigue combat	2	
Fatigue combat and malaria	1	
Probable paroxysmal tachycardia	1	
	4	
Tachycardia, simple—but found to be due to:		
Anxiety neurosis	1	
Neurocirculatory asthenia	1	
Fatigue and recurrent malaria	4	
	6	
Paroxysmal tachycardia (none proved but with characteristic history)		5
Extrasystoles		2
Auricular fibrillation (probable)		1
Auricular fibrillation (proved by ECG)		1
Hypotension (not confirmed on the ship but associated with recurrent malaria)	1	
SUMMARY (PROVED CASES PLUS FOUR CORRECTED DIAGNOSES)		
Valvular disease and acute endocarditis		5
Functional cardiac disorders:		
Effort syndrome and neurocirculatory asthenia		16
Paroxysmal tachycardia		6
Premature beats (extrasystoles)		2
Auricular fibrillation		2
Degenerative cardiovascular disease:		
Arterial hypertension		6
Coronary heart disease		6
Arteriosclerotic heart disease (questionable)		1
Coronary thrombosis		4
Angina pectoris		7
		55
Patients admitted with established diagnoses of, or suspected of having, cardiovascular disease but considered not to have these conditions*		48
Percentage of total evacuated patients probably attributable to cardiovascular disease		0.6

*Discrepancies between figures in this group and those in Table I are due to changes of diagnosis during observation aboard ship but do not alter the percentage of patients finally determined as having true cardiovascular disorder.

pital ship. It will be seen, however, that the independent study of the two authors confirms the approximate incidence of cardiovascular disease in the South Pacific area.

The discharge diagnoses from the Base Hospital are shown in Table III.

Rheumatic Fever.—A comparison of the incidence of rheumatic fever aboard the hospital ship and at the Base Hospital shows 22 cases on the former (0.24 per cent), and 14 cases at the latter activity (0.1 per cent). It is considered that the former figure is too high and only an approximation, since prolonged observation is often necessary to establish this diagnosis, and study with the electrocardiograph and sedimentation rate

TABLE III

INFECTIONS AND CONGENITAL HEART DISEASE		
Valvular heart disease		7
Mitral insufficiency	3	
Mitral stenosis and insufficiency	1	
Aortic stenosis	1	
Aortic and mitral stenosis and insufficiency	2	
Myocarditis—chronic rheumatic		1
Acute bacterial endocarditis		1
Congenital heart disease—interauricular septal defect		1
DEGENERATIVE HEART DISEASE		
Arterial hypertension		25
Thrombosis of coronary artery		3
Coronary heart disease		5
Angina pectoris		1
FUNCTIONAL CARDIAC DISORDERS		
Effort syndrome		23
Tachycardia		12
Paroxysmal auricular tachycardia		4
Auricular fibrillation		3
Premature beats (extrasystoles)		2
Total		88
Percentage of cardiovascular cases in 13,000 admissions		0.67

is difficult, if not impossible, at sea. Such studies were undertaken at the Base Hospital and showed a low incidence of rheumatic fever, but confirmed other observations of the occurrence of rheumatic fever in the tropics. All attacks in patients on the ship appeared in the tropics, as did most of those in the Base Hospital, although some appeared in personnel stationed in New Zealand.

It is of interest that the admission rate of adults with rheumatic fever to the Wellington Public Hospital, Wellington, New Zealand, in the years 1939 to 1942 is 0.3 per cent in spite of a wet, windy, cold climate. The admission rate for children is 0.9 per cent.*

DISCUSSION

This analysis emphasizes a few practical points. Though it may mention certain diagnostic errors, it must be considered in no sense a criticism of the diagnostic efforts of the combat medical officers. The authors are fully aware of the difficulties of such duty, and of the necessity for the use of the term "diagnosis undetermined" in many instances. However, when under the stress of battle or the burden of tropical exposure and malaria, the heart is apt to be blamed for fatigue and a multitude of chest complaints of which it is not culpable. The major reason for avoiding unproved cardiac diagnoses is to prevent

*Figures secured through the courtesy of Dr. J. O. Mercer and Miss Ernestine Winstone, Department of Pathology, Wellington Hospital.

accentuating cardiac neurosis and heart consciousness which are so prominent in rehabilitation problems.

Valvular heart disease has been rare in our experience, eleven cases in over 22,000 observations. Surely the elimination of men with this condition has been satisfactorily accomplished at enlistment, induction, and training centers. The problem of screening out those with a past history of rheumatic fever is far more difficult, but the recrudescence of the disease, under conditions of exposure, even in the tropics, makes such an attempt advisable, as suggested by Master.* Certainly men developing rheumatic fever in the Service should not be retained except under unusual circumstances. The increasing importance of it in training areas has been recently pointed out by Dr. T. Duckett Jones.

Greater caution should perhaps be employed in the elimination for overseas duty of men in the older age periods. Most cases of *persistent hypertension* are found in the older men. On the hospital ship, five out of eight were over 35 years of age, and of these three were chief petty officers and one a warrant officer in their forties and fifties. The emotional hypertension of combat conditions in younger individuals usually responds rapidly to rest and freedom from responsibility in a noncombat area. When it does not, and the physical and laboratory findings are normal, a deeper anxiety state must be suspected, and the man must be evacuated home as he will probably not be efficient in the combat area again.

The age of patients on the hospital ship, with the diagnosis *coronary heart disease* and *angina pectoris* ranged from 40 to 53 years. The ages of those with *coronary thrombosis* were 37, 42, 48, and 49 years. Angina tended to be overdiagnosed in various fatigue and anxiety states in young individuals and the final figure of those on the ship may even be too high.

The inaccurate portmanteau diagnosis *myocarditis* was overworked. It should not be used to mean coronary heart disease nor as a catchall for various sorts of vague chest and respiratory symptoms; but, if used at all, it should refer to an inflammation of the heart muscle as seen in rheumatic fever or diphtheria. It is usually a diagnosis which obscures rather than enlightens.

Effort Syndrome and Neurocirculatory Asthenia are less frequent than in World War I. Sufferers from these conditions appear to be better eliminated early during recruiting or training. Gastrointestinal disorder appears to be the organ neurosis of World War II.

Sinus *tachycardia* usually means anxiety, fatigue, heat exhaustion, anemia, or malaria. No case of thyrotoxicosis has been seen. In certain instances, however, sinus tachycardia has persisted without adequate explanation. Such patients, like those with persistent unexplained hypertension, are no longer valuable in a combat area.

*Comdr. Arthur M. Master, M.C., U.S.N.R., Rheumatic Fever in the Navy, U. S. Nav. M. Bull. 41: 1019, 1943.

SUMMARY AND CONCLUSIONS

During the period July 1, 1942, to July 1, 1943, 9,085 patients (Army, Navy, and Marines) were admitted to the hospital ship U.S.S. -------, acting as an evacuation ship for casualties from the Solomon Islands, New Hebrides, and New Caledonia. In this year, only 55 patients were found to be suffering from valvular heart disease, degenerative heart disease, or functional disorders of the heart. This is an incidence of 0.6 per cent. Forty-eight others, in whom cardiovascular disease was suspected, were found to have no evidence of such disorders but were suffering from other conditions, usually anxiety, fatigue, and malaria, with indefinite physical signs and symptoms. Twenty-two patients with rheumatic fever were evacuated during this period (0.24 per cent).

During the same year, 13,000 admissions (including all readmissions) were made to U.S. Naval Mobile Hospital ---------- (later U.S. Naval Base Hospital -------), in New Zealand. A similar study shows that 88 patients were suffering from organic, or disabling functional, cardiac disorders—an incidence of 0.67 per cent. Rheumatic fever occurred in 0.1 per cent of the total.

Typical effort syndrome and neurocirculatory asthenia, while still important, appear to be less common than in World War I. Part of this is due to these syndromes being absorbed into neuropsychiatric diagnoses without emphasis on the circulatory system. However, even in such instances, we have been impressed with the relative infrequency of the classical picture of cardiovascular instability as the presenting and disabling symptom complex.

This survey indicates that elimination of men with heart ailments is being satisfactorily accomplished in enlistment, recruiting, induction, and training areas.* Somewhat greater caution should be observed in assessing the cardiovascular status of older men in the determination of fitness for overseas and combat duty. The unsubstantiated diagnosis of cardiovascular disease in naval and military personnel on combat duty, and especially in fatigue states, should be avoided to prevent the development of cardiac neurosis and invalidism.

*It should be noted that the figures in this paper are based largely on an experience with carefully selected, volunteer troops, preponderantly marine and naval personnel, in whom physical defects should be minimal.

SOME PRACTICAL ASPECTS OF THE RHEUMATIC FEVER PROBLEM WHICH HAVE AN IMPORTANT BEARING IN MILITARY MEDICINE

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GENERAL interest in rheumatic fever in the past few years has developed in proportion to the increased practical knowledge of the disease. However, for many years, we have lagged sadly in the development of programs for the care of rheumatic fever patients and in having rheumatic fever accepted as a public health problem. Physicians in England have been far more active than we in developing programs, such as providing beds for the treatment of these patients at public expense, making rheumatic fever a reportable disease, etc. Impetus in this country has developed largely as the result of small programs in a few states, instituted by the Children's Bureau of the United States Department of Labor. These carefully worked out plans, along with the study and care programs conducted by private agencies in a few large cities, represent pioneer work. Limitation of funds and of availability of trained medical, social service, and nursing personnel are distinct deterrents at present to the rational extension of these programs. As the medical profession becomes more aware of the various features of the rheumatic fever problem, it would seem almost certain that they will insist upon broadening the scope of some of the present studies and programs by both private and public agencies.

At present, the country is in an "all out" war, with millions of men dislocated from their usual vocations and mode of living. For military purposes, it is essential that these men go through a herding experience quite unlike that experienced by the usual adult in time of peace. It is hence not surprising that epidemic infectious diseases occur. Variations in the presence and distribution of pathogens, population susceptibility, exposure, crowding, and many other factors influence considerably the disease patterns resulting in different groups of service men.

In addition to the large number of nonmedical personnel dislocated from civilian life by war, the medical profession has been proportionately called into service. Many physicians have been obliged to become proficient in the care and prevention of diseases far different from those encountered in their former medical experience. Many physicians who have had but little practical contact with the disease are now caring for patients with rheumatic fever and rheumatic heart dis-

From the House of the Good Samaritan, Boston, Mass.

ease. Often, the experience of these physicians has been limited to that which they gained as students or interns. This experience usually was restricted to the care of the acute rheumatic fever case and the evaluation of heart murmurs. Opportunity to observe these patients over long periods of time and to study the varying influences affecting the outcome of the individual patient has been afforded only a limited number of workers.

Having spent, with a group of active collaborators, some years studying various aspects of the rheumatic fever problem, we think it advisable to present an attitudinal review which may help to define the problem in the minds of physicians confronted with the care and disposition of patients with rheumatic fever. No attempt will be made to make this summary definitive or bibliographic. The same fundamental features hold, regardless of whether the Armed Forces or civilians are concerned, although the former raises many additional problems of a serious nature. No new concept is to be presented. The details and references to substantiate nearly all statements can be found in Paul's "Epidemiology of Rheumatic Fever (1943)," prepared and distributed at the request of the American Heart Association, and published through the cooperation of the Metropolitan Life Insurance Company. Although many questions remain to be answered, various investigations, at present being carried out by both military and civilian personnel, will doubtless add much to our basic knowledge, especially in the field of prevention.

THE ETIOLOGY OF RHEUMATIC FEVER

Perhaps no single statement concerning rheumatic fever would receive such universal medical agreement as one to the effect that the cause of the disease is unknown. While it is essential to state this early, and, further, to indicate that much basic work remains to be performed in this field, our knowledge of the natural history of rheumatic fever is not inconsiderable. We need not wait for further knowledge in order to develop programs of care and prevention. Dr. Homer F. Swift, long a student of rheumatic fever, has repeatedly stressed this, and we feel that investigators such as Coburn, Wilson, Kuttner, and others would agree, although each might stress various features, dependent upon their own particular experience and beliefs.

To review all of the suggested theories as to etiology would not seem relevant. Recently, there have appeared two suggestions concerning etiology. One theory reiterates the allergic hypotheses without any new data. The second theory is based on the observation that, in the rat, severe overdosage with desoxycorticosterone acetate produces lesions similar to those seen in periarteritis nodosa, malignant hypertension, and rheumatic fever. It is suggested that infections or exposure result in an abnormal (probably excessive) adaptive response of the adrenal

cortex, and, hence, rheumatic fever may be partly a disease of adaptation. These ideas need further study, interpretation, and correlation with known facts.

All observers agree to the high familial incidence of rheumatic fever, and increasing evidence points to an hereditary susceptibility.

The relationship between group A, beta-hemolytic streptococcal respiratory infections and rheumatic fever is well established, but many features concerning this relationship need clarification. For example, the antigen-antibody reaction, variations in types of hemolytic streptococci, and factors possibly influencing pathogenicity and epidemicity, need further study. Of primary importance would be the experimental reproduction of the disease or its counterpart, in an experimental animal. Some of these features are receiving attention now, while others must await a return to more leisurely study in a postwar world. Despite the need for these studies, present known facts about rheumatic fever are of practical value, and these will be stressed. It is believed that further knowledge will serve to clarify present accepted observations, and hence explain and extend rather than disprove them.

RHEUMATIC FEVER AS AN EPIDEMIC DISEASE

Epidemiology in recent years has become broadened by general usage. The medical and lay public apparently have preferred to persist in defining as epidemic disease only those great scourges representing an highly virulent agent producing great volumes of disease among highly susceptible peoples. The influenza epidemic of World War I is an example par excellence. The communicable diseases of childhood are also accepted. Only a limited number of workers, however, speak of the epidemiological pattern of noninfectious diseases, such as pellagra, and such a condition as mottled enamel. Scarlet fever is not only considered an epidemic disease, but too frequently as the only serious phase of the hemolytic streptococcus problem. This is reflected in the laws governing quarantine of scarlet fever cases, while infections without scarlatinal rash, even though caused by the same type of group A beta-hemolytic streptococcus are not restricted and often not even segregated. It is slight wonder that rheumatic fever, a disease which follows closely the epidemiological pattern of hemolytic streptococcal infections, is not considered an epidemic disease. Few physicians think of an epidemiological pattern in connection with this disease, save in relation to poor housing, crowding, and low economic level.

Ever since World War I, and especially in the past twelve years, numerous reports have stressed the association between hemolytic streptococcal tonsillitis and pharyngitis and the subsequent development of rheumatic fever. Coburn, more than any worker in this country, has emphasized this relationship. The relationship of rheu-

matic fever to hemolytic streptococcal respiratory infections has been reported by many English workers. Many hemolytic streptococcus epidemics have been recorded in rheumatic fever institutions and convalescent homes, with as many as 50 per cent of these having the epidemic infection developing a recurrence or recrudescence of rheumatic fever within two to three weeks. We may ultimately learn why these percentages vary with each epidemic, but one must accept that some relationship does exist. The grouping of hemolytic streptococci by Lancefield, and the later typing of group A strains by Griffith and by Lancefield have offered a new epidemiological tool with which to study the problem. The reports of Kuttner, Coburn, and others, as well as unpublished data from the House of the Good Samaritan are all in essential agreement. In a population where all are known to be rheumatic fever susceptible (by the presence of low-grade rheumatic fever or recent recovery from rheumatic fever), infections with certain types of hemolytic streptococci are associated with a varying number of recurrences of the disease. The strains causing trouble are usually epidemic in behavior and usually spread rapidly. The types of group A hemolytic streptococci may vary from year to year. It has been our experience that approximately one-third of the rheumatic fever recurrences are not preceded by a clinical hemolytic streptococcal infection, but careful and frequent throat cultures usually indicate that there has been a previous change in the type of hemolytic streptococcus in the throat, or a change from a negative to a positive throat culture.

To one who has not yet accepted the possibility that hemolytic streptococcal infections and/or some peculiarity in the immune reaction to such infections, is the entire mechanism in the causation of rheumatic fever, the close clinical, bacteriological, and immunological (antistreptolysin response) correlation between hemolytic streptococcal infections and rheumatic fever has consistently been viewed with skepticism. However, it seems reasonably certain to us that, despite the need of further knowledge, the importance of this association cannot be denied or dismissed.

It is much easier to demonstrate an association between hemolytic streptococcal infections and rheumatic fever, than to disprove it. Since instituting protective measures against the spread of hemolytic streptococcal infections in a rheumatic fever hospital, our rheumatic fever disease patterns have altered. In our experience, fatalities caused by rheumatic fever have been strikingly associated with increased severity of the disease following an hemolytic streptococcal infection. It has not been unusual to see fulminant, fatal rheumatic fever follow a hemolytic streptococcal infection, despite a good recent recovery from rheumatic fever with only minimal residual heart disease. Protection from hemolytic streptococcal infections has resulted in a disappearance of such catastrophies.

During a period of four years, we have observed several instances of increased cardiac failure without any definite evidence of preceding hemolytic streptococcal infection. Although such increase in failure is usually due to an associated increase in rheumatic fever activity, there was no other evidence of this in these cases. We have also observed the development of chorea in patients who had apparently recovered from rheumatic fever and who showed no evidence of antecedent hemolytic streptococcal infection. All of these apparent rheumatic fever recurrences occurred more or less simultaneously during a short period of three to four weeks. This information is included merely to indicate that all problems are not answered. With these exceptions, it has been our experience that, provided the early stages of rheumatic fever do not prove fatal, our patients have recovered after varying periods of time and with varying degrees of residual heart damage, unless hemolytic streptococcal infection has intervened. Hence, in our experience, rheumatic fever following hemolytic streptococcal infection is the major problem.

From a study of the literature, it seems likely that most initial attacks of rheumatic fever are closely associated with hemolytic streptococcal infections. Further, once an individual has had definite rheumatic fever, the vast majority will do well unless an hemolytic streptococcal infection occurs. The above observations are based on clear-cut diagnoses of rheumatic fever. Many individuals present the problem of rheumatic heart disease, even with failure, in adult life, and deny earlier rheumatic fever. In our experience, those patients with insidiously developed rheumatic heart disease (usually with mitral stenosis), from families who know the patterns of rheumatic fever because of disease among other members, have but little, if any, cardiac enlargement. These patients have universally done well unless rheumatic fever intervenes. Appreciable degrees of cardiac hypertrophy have been found only as the result of recognizable rheumatic fever. This is an interesting group of patients from which we may learn much, but it has consistently been evident to our group of workers that the seriously disabled rheumatic heart disease patient, if carefully studied, is found to have, or to have had, active rheumatic fever, usually at a clinically recognized level.

Recent English reports of studies on military personnel, and reports from military sources beginning to appear in this country, stress the fact that in the Armed Forces the rheumatic fever pattern is closely associated with the hemolytic streptococcal problem. While other factors, such as exposure, dampness, and chilling, may play a role, no report has failed to express the coexistence of throat infections, such as tonsillitis or pharyngitis, and even scarlet fever. While clinical diagnoses are not entirely reliable with regard to the etiological classification of respiratory infections, the presence of scarlet fever can be

taken to indicate that hemolytic streptococcal infections are present. Wherever there has been corroboration of clinical diagnoses of respiratory tract infections by bacteriologic examination, it has been found that the hemolytic streptococcus is present and apparently pathogenic when rheumatic fever begins to appear. Grouping and typing of these organisms throws additional light on the problem. Epidemic types or those pathogens which spread easily are usually found to be the troublemakers, despite the presence of a number and variety of types, of seemingly low pathogenicity in the same population. The carrier rates may vary considerably from season to season, even without any appreciable volume of streptococcal illness. However, when a given type of streptococcus begins to cause illness, this type will increase in the general exposed population, and the resultant illness pattern will be determined, at least to a large extent in an intimately exposed population, by the pathogenicity of the organism and the susceptibility of those exposed. From the available reports, it seems obvious that rheumatic fever occurs in variable degrees in the majority of, but not in all, hemolytic streptococcus epidemics. We do not yet know the influence of the streptococcus types, and other streptococcal biologic features, on the development of rheumatic fever, but it does seem apparent that rheumatic fever, in a population of unknown rheumatic fever susceptibility, occurs in direct relation to the volume of streptococcal illness. The rates will doubtless vary in different parts of the United States and the world, and there are doubtless many unknown factors affecting these rate variations. For instance, reports of rheumatic fever during streptococcal infections among young British naval personnel are the highest rates yet recorded. In addition to the volume of hemolytic streptococcal illness, other factors which may possibly influence the occurrence of rheumatic fever are: the evidence of a previous rheumatic fever history (this will be discussed in more detail further on), unknown host features, associated or previous virus invasion, and variations in the biology of hemolytic streptococci.

In military personnel, just as in the studies on known rheumatic fever populations, there is a consistent association between rheumatic fever and previous infection of the respiratory tract with the hemolytic streptococcus. This correlation holds from clinical, bacteriological, and immunological (antistreptolysin response) points of view. A high percentage of these patients give a definite history of sore throats (often with hemolytic streptococci isolated from the throat) ten to twenty-one days before, but in some this is absent, and only the antistreptolysin response curve gives a clue to the previous infection. This closely parallels the pattern in known rheumatic fever populations, and indicates that nonclinical, but definite invasive streptococcal infections occur. This has long been recognized from studies on streptococcal epidemics in well children.

Since the clinical diagnoses of respiratory tract infections are inaccurate without laboratory confirmation, the basis of any rheumatic fever program should be bacteriologic. Careful bacteriologic study of respiratory infections from any given epidemiological group should give the clue to the illness pattern developing, and offers the best hope of any prevention program. Thus, in order to anticipate the development of a streptococcal disease problem in any military establishment, it is first necessary to divide the population into epidemiological units, each of which is composed of individuals living together and having the same exposure periods. An accurate and continuous record must be kept of all clinical respiratory infections. Finally, the percentage of throat cultures that are positive for hemolytic streptococci must be determined on adequate samples of both the clinically ill and well individuals, composing each of these separate epidemiological units. Grouping and typing of all positive cultures will provide additional information of value.

To a medical ward officer receiving rheumatic fever patients for care from a wide variety of groups in his station or even different stations, the problem must indeed be confusing. Only when one realizes that, for each of these patients, there have previously existed many hemolytic streptococcal infections, can one begin to focus at the point where this patient's problem could have been attacked.

SUSCEPTIBILITY TO RHEUMATIC FEVER

There can be little doubt but that the familial incidence of rheumatic fever is high, and most reports indicate that multiple cases of rheumatic fever in a family are as frequent as found in the case of tuberculosis. The recent work of Wilson, Taussig, and their collaborators has strengthened the available data relative to hereditary susceptibility. While much needs to be learned in this field, the data which are accumulating strongly indicate the importance of a probable hereditary susceptibility. These data are doubtless important, but do not obviate the importance of a variety of other features in relation to the initial or repetitive development of rheumatic fever.

There can be no doubt but that one attack of rheumatic fever renders an individual susceptible to subsequent attacks. As indicated previously, many investigators, among them ourselves, feel that there is an association between these initial as well as repetitive attacks and infections with the hemolytic streptococcus.

No adequate data are available as to the number of susceptibles in the general population. Should such data become available, there would doubtless be considerable variations in a country with such marked climatic differences as the United States. This is suggested by present available information indicating a considerable sectional difference in incidence of rheumatic fever and heart disease. In fact it seems

reasonable to speak of high and low incidence areas, despite a lack of accurate incidence studies and knowledge of the many factors which might be responsible for such variations. It seems reasonable, as an estimate, that perhaps 2 per cent of our young adult population may prove to be susceptible to rheumatic fever as indicated by a definite history of the disease.

Reports already appearing in the medical literature indicate that there may be considerable variation with regard to the frequency of an history of previous rheumatic fever among those men developing the disease in military service. Some of these reports indicate a previous history in as high as 50 per cent of the rheumatic fever patients.

It becomes obvious from a practical point of view that the rejection of such men with a previous history would decrease the problem of rheumatic fever in the Armed Forces. Other practical points, however, must be considered and determined by military authorities. The mere administrative problems inherent in verifying any disease history in as many as 2 per cent of the applicants for military service are tremendous. When one considers that those anxious to perform military service could easily deny previous rheumatic fever, and that malingering by those desiring to escape military service may be common, the inherent practical problem becomes enormous. Furthermore, the rejection of susceptibles on a basis of history, if practical, would at best eliminate only one-third to one-half of the rheumatic fever cases in the Armed Services. The ultimate decision would seem rationally to be based on the administrative difficulties inherent in rejection of such applicants and the practicability of the development of preventive programs. However, opinions will doubtless vary greatly. It seems logical that the individual of unknown susceptibility deserves protection against the development of rheumatic fever just as much as those known to be susceptible by verified history. In consideration of the need for man power and the possible development of prevention programs (to be discussed later), it is suggested that we accept the responsibility of attempting to prevent hemolytic streptococcus epidemics in areas of high rheumatic fever incidence regardless of whether history susceptibles be accepted for service or not.

RHEUMATIC FEVER PREVENTION PROGRAMS

There are many possibilities relative to the development of such programs, and much is to be learned from a variety of organized attacks upon the problem. Should it be possible from an administrative point of view to direct the location of known susceptibles or of those developing rheumatic fever in the Service to low incidence areas, some preventive or prophylactic results might be expected. This is clearly an important administrative problem for the Armed Services.

Since rheumatic fever is outstandingly prevalent during hemolytic streptococcus epidemics, one naturally turns to the prophylactic use of

the sulfonamide drugs as being perhaps the most important feature of any program. There seems to be general agreement that once rheumatic fever has begun, the sulfonamides are ineffective (at least sulfanilamide and sulfapyridine) and may be harmful. There also seems to be general agreement that once a hemolytic streptococcal infection has begun, subsequent rheumatic fever cannot be avoided by the use of these drugs. It has been suggested that sulfonamides given after the onset of hemolytic streptococcal infection may even increase the possibility of development of rheumatic fever, although no substantiating data have been presented.

A number of reports have appeared in the last two or three years indicating that sulfanilamide given in small prophylactic doses to patients with previous rheumatic fever will prevent the development of hemolytic streptococcus infections and hence recurrent rheumatic fever. There seems no dissenting voice to this, but as yet no reports have reached the literature relative to the effectiveness of the less toxic sulfonamides. It has been indicated that a small percentage of individuals are unable to take such prophylactic agents because of sensitivity, and there are yet many features to be worked out. For instance, we do not yet know what the long-time administration of these drugs will do with regard to the development of sensitivity. Neither do we know whether drug-resistant strains of hemolytic streptococci will be developed as a result of such programs, or the effect on the rheumatic fever patient of infection with such drug-resistant strains.

Numerous reports are available relative to the effectiveness of sulfonamides in the control of the meningococcus problem. Cases may be abruptly terminated and carrier rates lowered. There are also reports indicating that the spread of streptococcal infections may be curtailed by the use of chemotherapeutic agents. Less is known concerning the effect on pathogenicity and the carrier state of streptococcal as compared to meningococcal infections. There seems, however, but little doubt that it is possible to affect the epidemic streptococcal pattern by the use of these agents.

Many features warrant careful study. The choice of the particular agent is not yet determined, nor the dosage, nor the exact method of administration. The comparative value of a small daily dosage over a long period of time as opposed to larger amounts of the drug given over a short period is not yet determined.

In view of the considerable variations in the spread of hemolytic streptococcus within different epidemiological units, one should be careful to avoid wholesale administration of such agents as the sulfonamides. It should also be pointed out that a false sense of security may be developed by confusing seasonal, annual, and unit streptococcal infection variations for drug effects.

Because of these possible misinterpretations of results, and because of the possible dangers of developing sulfonamide sensitivity and drug-fast strains, one should be reticent in too readily accepting the wholesale and uncontrolled administration of these drugs.

In recent years, interest in the possible value of salicylates for rheumatic fever has reawakened. Several reports suggest that the protracted daily administration of salicylates starting at the time of a hemolytic streptococcal respiratory infection may in some way greatly decrease the probability of developing subsequent rheumatic fever. This is in keeping with the recent suggestion that the intravenous administration of large amounts of salicylate (resulting in a high continuous salicylate plasma level) may, if begun early in the course of the disease, advantageously affect the outcome of rheumatic fever. It has been further suggested that the daily administration of egg yolk may result in the curtailment of the development of rheumatic fever recurrences. These are mentioned as features requiring further study and analysis.

Control measures other than the use of drugs also need careful evaluation. There can be little doubt that the segregation of hemolytic streptococcal infections may alter the pattern of disease in any given population. In the past, scarlet fever patients have been the only ones given appreciable attention. Scarlet fever comprises only a very small and varying proportion of all hemolytic streptococcal respiratory infections. Furthermore, clinical diagnoses alone are a poor index of hemolytic streptococcal illness. Therefore, if segregation is to be done in an advantageous way, it is necessary to do careful bacteriologic studies on all patients with respiratory disease. In addition to determining which patients have positive hemolytic streptococcus cultures, it is of value to group and type the isolated organisms in order to identify the pathogenic strains.

Literature reports suggest that, on an open scarlet fever ward, an individual patient maintains his infectious type for eight to ten days, thereafter frequently becoming a carrier of other types of streptococci to which he is exposed. Nevertheless, we do not know how long hemolytic streptococcal respiratory disease cases should be segregated. In order to answer this question intelligently it will be necessary to know whether individuals developing a carrier state without becoming clinically ill are infectious and just how long strains carried in the throats of recovered clinical cases remain virulent. It will also be necessary to learn more about the effect of sulfonamide therapy on the duration of the carrier state and on the virulence and spreading tendencies of hemolytic streptococci.

The nature of the living quarters in a military establishment may influence the spread of respiratory disease. It seems likely that exposure during sleeping hours is particularly important. There is evidence

which suggests that the volume of disease is influenced more by the number of individuals sleeping in a given room than by the area of floor space or the number of cubic feet of air space allotted to each man.

Other possible hemolytic streptococcus control measures which need further investigation are ultraviolet radiation and the use of aerosols.

To reiterate, the prevention of rheumatic fever, within the limits of our present knowledge, depends apparently upon the successful prevention of hemolytic streptococcal infections. In any given group or unit, the key to the development of such a problem rests with the careful bacteriologic study of individuals developing respiratory infections. Careful study may reveal the presence of an increasing hemolytic streptococcal disease rate long before the peak is reached, and so indicate the need of instituting preventive measures. It is hoped that in the near future we will have sufficient additional knowledge so that we will know what measures will safely prevent a maximal amount of illness, with a minimal use of chemotherapeutic agents and a minimal disruption of routine military programs.

PSYCHOLOGICAL FACTORS

One cannot help but be impressed with the inherent opportunities for the development of psychological difficulties in those individuals with rheumatic fever and its attendant rheumatic heart disease. Neurocirculatory asthenia is found to be common in adults with rheumatic heart disease. It has often impressed us that the old adage, "A little learning is a dangerous thing," is most appropriate. This is small wonder when one considers the amount of teaching done in the presence of rheumatic fever patients and the general inclination of physicians to stress the heart disease factors above all else.

Only those rheumatic fever subjects developing serious degrees of heart disease become actual cardiovascular cripples, or have a fatal outcome by mid-adult life. This group comprises a small percentage of the total rheumatic fever cases. Not only are these progressive cases with a poor outlook small in relative numbers, but they usually become defined early in the course of the disease.

Since the incidence of serious heart disease following first attacks of rheumatic fever in adult life is smaller than that in children, it seems even more necessary to orient carefully the patient with regard to the problem, and prevent his overready acceptance of the fact that heart disease will become serious. It is hard to make this clear when policies vary with regard to the handling of those rheumatic fever subjects who either escape detectable heart disease or develop only slight degrees of cardiac damage. Apparently the susceptibilities of these two groups are similar. After suitable convalescence and reasonable rehabilitation, there seems little difference in the ultimate outcome of those individuals who have functionally good hearts, regardless of the pres-

ence or absence of slight cardiac enlargement and certain murmurs. Physical activity seems to have little effect on their ultimate prognosis, once the disease has become definitely inactive. Protection of these individuals against hemolytic streptococcal respiratory infections should be the most important part of any program designed for the promotion of their well-being. It is believed that the explanation of such features to rheumatic fever subjects by physicians will result in fewer psychological problems and a more active interest on the part of the individual in attempting to avoid exposure to hemolytic streptococcal infections.

It is rather surprising that, in a child of average intelligence, good cooperation may be obtained with regard to long bed rest, even in the presence of reasonable well-being, providing the child becomes aware of the fact that he is being restricted temporarily because of an active disease process and for the purpose of minimizing the amount of permanent heart damage sustained. In the past, we have encouraged children well over the active stage of the disease to return to active physical lives even in the presence of moderate degrees of heart disease. As yet, we have seen no harm result from this program. The patients getting into difficulty have done so, not as a result of physical activity, but because of hemolytic streptococcal infections.

PROBLEMS RELATIVE TO THE DISPOSITION OF RHEUMATIC FEVER PATIENTS IN THE ARMED SERVICES

The need for man power, especially the services of highly trained members of the Armed Forces, must of necessity dictate the ultimate disposition of those service men developing rheumatic fever. This problem is a difficult one with many aspects. As indicated before, a previous history of rheumatic fever results in an increased likelihood of an individual developing rheumatic fever, provided he is stationed in an area of high rheumatic fever incidence. So, too, will those individuals developing the disease in the Service for the first time show an increase in susceptibility to further attacks. The number of individuals developing incapacitating degrees of heart disease and progressive rheumatic fever will doubtless be small.

The presence or absence of heart disease following an attack of rheumatic fever may determine whether or not an individual is eligible for compensation and, therefore, may influence policies of disposition. Otherwise, the disposition of rheumatic fever cases should not depend upon whether such individuals develop slight degree of heart disease or fail to acquire any detectable cardiac damage. Both groups of individuals will be likely to develop repetitive rheumatic fever if they are exposed to hemolytic streptococcal respiratory epidemics, and hence it seems reasonable to handle them both in the same manner.

When programs of protection against hemolytic streptococcal infection are developed, the majority of these men can be of continued value to the Service without jeopardizing their health. Such programs need exploration and careful study. They will require trained personnel, but there can be little doubt of their importance and ultimate service in man-power saving and disease prevention.

What will eventually happen to men who have developed rheumatic fever for the first time while in the Armed Services is of importance. However, we do not at present know the actual natural history of rheumatic fever beginning in adult life. By adequate follow-up of the veterans of World War II we may learn whether there is any difference in the fundamental process when rheumatic fever appears for the first time at various ages, or whether variations in outcome are entirely dependent upon exposure to streptococcal respiratory infections and development of natural immunity to the hemolytic streptococcus. Many such features need clarification.

SUMMARY

Although the etiology of rheumatic fever is unknown, our knowledge is sufficient to warrant the development of programs of care. The close relationship between epidemic hemolytic streptococcal infections and rheumatic fever is discussed, and it is pointed out that rheumatic fever in a given population follows closely the epidemiology of hemolytic streptococcal infections. This pattern is so convincing that it forms the basis of prevention programs. Prevention programs are discussed, with especial emphasis on the careful study of respiratory infections from a bacteriologic point of view. Culturing, grouping, and typing of such infections offers a key to the streptococcus problem in a given epidemiological unit. The use of sulfonamides prophylactically is discussed. Other preventive measures than chemotherapy are mentioned.

The general problem of susceptibility, as well as considerations relative to the disposition of rheumatic fever patients in the Armed Services, are evaluated. Caution against developing an unfavorable psychology in rheumatic fever patients is emphasized. Numerous gaps in our knowledge are enumerated throughout the report.

A plea is made to accept the problem as perhaps the most serious feature of the general hemolytic streptococcal problem, and some measures are discussed which may be helpful in the prevention of rheumatic fever. The authors are cognizant of the fact that, despite the close relationship with hemolytic streptococci, as indicated, there are many unsolved problems relative to the disease. These problems are by no means limited to the hemolytic streptococci association, but represent a wide variety of biologic aspects.

FOREIGN BODIES IN AND ABOUT THE HEART

MAJOR EDWARD F. BLAND, M.C.

DURING the first six months of operation of the Sixth General Hospital, U.S. Army, in the North African theater eight patients have been encountered with penetrating chest wounds and retained metallic foreign bodies either in, or in close apposition to, the heart. Similar cases will probably be observed with increasing frequency as the war progresses, and the question will arise as to whether or not surgical removal should be attempted.

Recorded data helpful in this connection are scant since this type of injury is largely limited to combat operations and, hence, its counterpart in civilian practice is rare. Therefore, we are recording in this preliminary report the clinical features and x-ray findings in four of this series because of their special interest.

In these case reports the clinical notes and x-ray findings of the various medical installations in the chain of evacuation have been incorporated with our own studies. We regret that exigencies of the military situation make it impossible to render at this time full credit by name to the various individuals and installations involved.

CASE REPORTS

CASE 1.—*Bullet in the Right Side of the Heart.*—A staff sergeant, aged 25 years, in the field artillery, was in a battery holding an exposed position near Tebourba, in Tunisia, when it was attacked by 35 enemy tanks, on Dec. 6, 1942. During the engagement he was wounded by machine-gun bullets. Shortly thereafter, in a nearby dressing station, he was found to have two wounds of entrance in the left pectoral region and a superficial wound of the left wrist. Sulfanilamide dressings were applied and he was evacuated to a British general hospital.

On arrival his condition was satisfactory. There were no abnormal physical signs, but x-ray examination revealed a metallic foreign body in the heart and another fragment in the soft tissue of the left chest wall. The latter fragment was removed two weeks after his injury and, thereafter, he appeared to be making a good recovery without symptoms or signs referable to the intracardiac bullet.

Six weeks after his injury he began to have aching substernal discomfort, aggravated sharply by deep inspiration, with accompanying radiation through to the back, to both shoulders, and occasionally to both arms as far as the wrists. He appeared pale and breathless, and the area of cardiac dullness was enlarged to the left. The lungs were clear except for the signs of compression at the left lung base posteriorly. Fluoroscopic examination showed the heart shadow much enlarged and the cardiac pulsations reduced in amplitude. The bullet appeared to be within the right border of the heart. His temperature rose to 101° F., and he was started on chemotherapy.

At the end of a week he was much improved, and on fluoroscopic examination the cardiac shadow had decreased in size. At the end of three weeks the heart was normal in size and pulsations. The position of the bullet remained unchanged.

Nine weeks after his injury he again became ill with right-sided pleural pain followed by a moderate effusion. Aspiration yielded 150 c.c. of opaque, sterile fluid. In the course of the next two weeks he recovered from this second complication. In March, 1943, he was seen in consultation by Col. E. D. Churchill who advised against surgical exploration for the retained bullet.

Four months after receiving his wound, and in the course of evacuation to the zone of the interior, he first came under our observation. By this time he appeared to have made a complete recovery. The chest wound was well healed and physical examination revealed no abnormalities in the heart or lungs. Fluoroscopic examination at this time confirmed the presence of a sharp-nosed bullet (caliber .30), measuring approximately 2.3 cm. in length, lying within the shadow of the right side of the heart (Figs. 1*A* and 1*B*). It moved vigorously with each heartbeat. Lateral and oblique views showed the bullet in the midlateral portion of the heart, placed slightly anteriorly and most likely at or near the junction of the right auricle and ventricle. By rotation of the patient it was impossible to separate the shadow of the foreign body from that of the heart to an extent greater than is shown in Fig. 1*A*. Fully two-thirds of the bullet appeared to be embedded in the wall of the heart, possibly in a much thickened pericardium. Incidentally, in the course of our x-ray studies an additional, and previously unsuspected, fragment of metal measuring 1 by 0.4 cm. was discovered buried in the central portion of the liver. An electrocardiogram, including Lead IV, was normal except for a slight degree of right axis deviation, which was considered by us within the normal range for a vertically placed heart.

In May, 1943, five months after his injury, he was returned to the United States. His only complaint was occasional substernal discomfort, a sense of pressure, radiating to the upper right arm. It usually lasted one to two hours and was uninfluenced by motion, position, or respiration.

Comment.—It is extraordinary that a missile of this size could have traversed the chest without causing serious injury to the vital mediastinal structures. Undoubtedly its force must have been largely spent before it entered from a lateral direction and presumably followed the anterior contour of the thoracic cage, to be deflected inward along the structural plane between the right lung and heart. The delayed appearance of pericardial and pleural effusions, six and nine weeks, respectively, after the injury, is of some further interest.

CASE 2. *Foreign Body in the Left Side of the Heart.*—Sergeant, aged 22 years, in a tank destroyer battalion, was wounded in action while advancing on foot near Fonduk in Tunisia, April 13, 1943. A comrade who was 6 feet ahead of him stepped upon an antipersonnel mine and he (the patient) was jarred backward by the resulting explosion. He experienced immediate dyspnea but no pain, and attributed his breathlessness to the concussion. Not realizing that he had been wounded, he continued forward a few paces until he almost fainted and discovered blood upon his shirt. At the battalion aid station he was found to have a penetrating wound between the fourth and fifth ribs in the left anterior

Fig. 1A.

Fig. 1B.

Fig. 1A.—Case I. Anterior-posterior view showing the bullet in the right wall of the heart.
Fig. 1B.—Case I. A left anterior oblique view of the bullet in the right wall of the heart.

axillary line. Dyspnea continued and he raised small amounts of bloody sputum.

The following day, at an evacuation hospital, x-rays revealed a foreign body in, or near, the apex of the heart, and an exploratory thoracotomy was performed. A small sucking wound was found, and 8 cm. of the anterior portion of the fourth rib were removed. The pleural cavity yielded 500 c.c. of fluid blood. A slow hemorrhage from the anterior surface of the lower lobe of the lung was controlled by suture. At this point the patient went into rapid shock and further search for the foreign body was abandoned. A tight closure of the pleura and chest wall was obtained, and shortly thereafter the patient's condition began to improve. Chemotherapy had been administered from the onset, and by the end of the sixth day his condition was such that evacuation to the rear was accomplished in easy stages without untoward reactions.

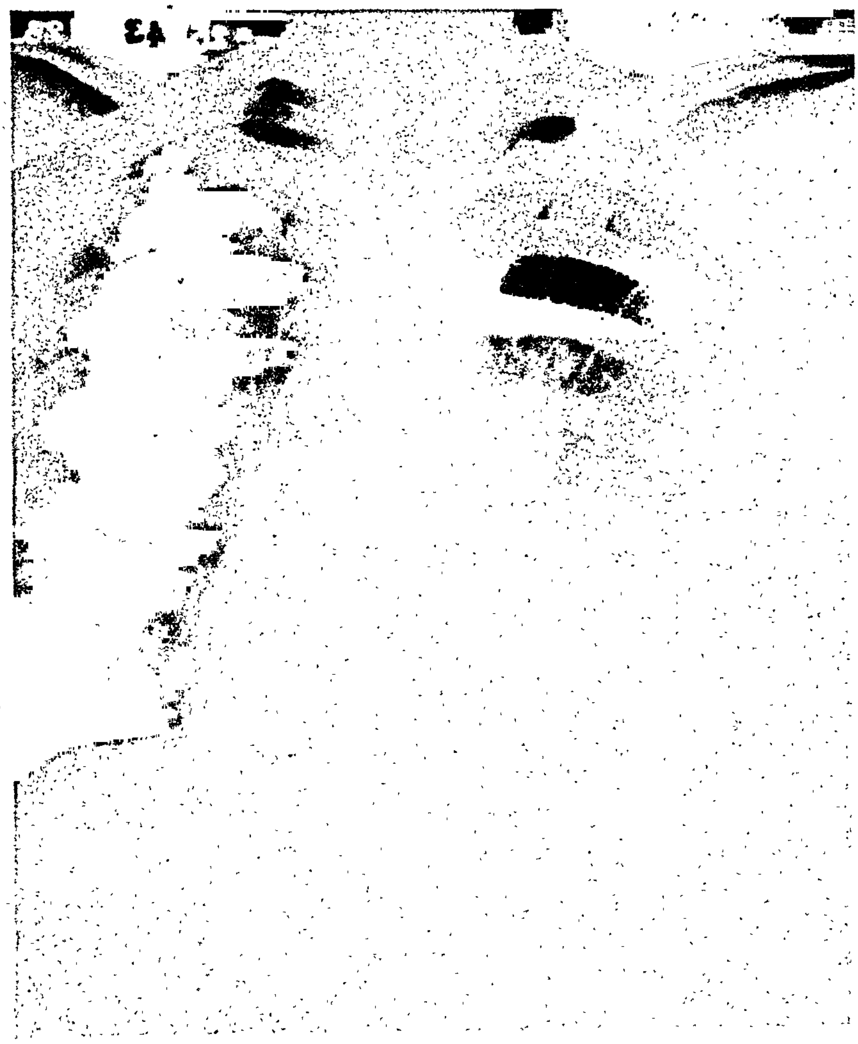

Fig. 2A.—Case 2. Roentgenogram taken at the time of the pericardial effusion. The bullet, visible at this time under the fluoroscope, well within the shadow of the heart, is not evident in this film.

Two weeks after the injury, while convalescing satisfactorily, he developed slowly increasing dyspnea at rest and a fever up to 102° F. Signs of fluid at the left base increased and pleural and pericardial friction rubs appeared. X-ray examination showed marked enlargement of the cardiac shadow as well as considerable pleural effusion (Fig. 2A). Fluoroscopically, the pulsations of the cardiac borders were feeble.

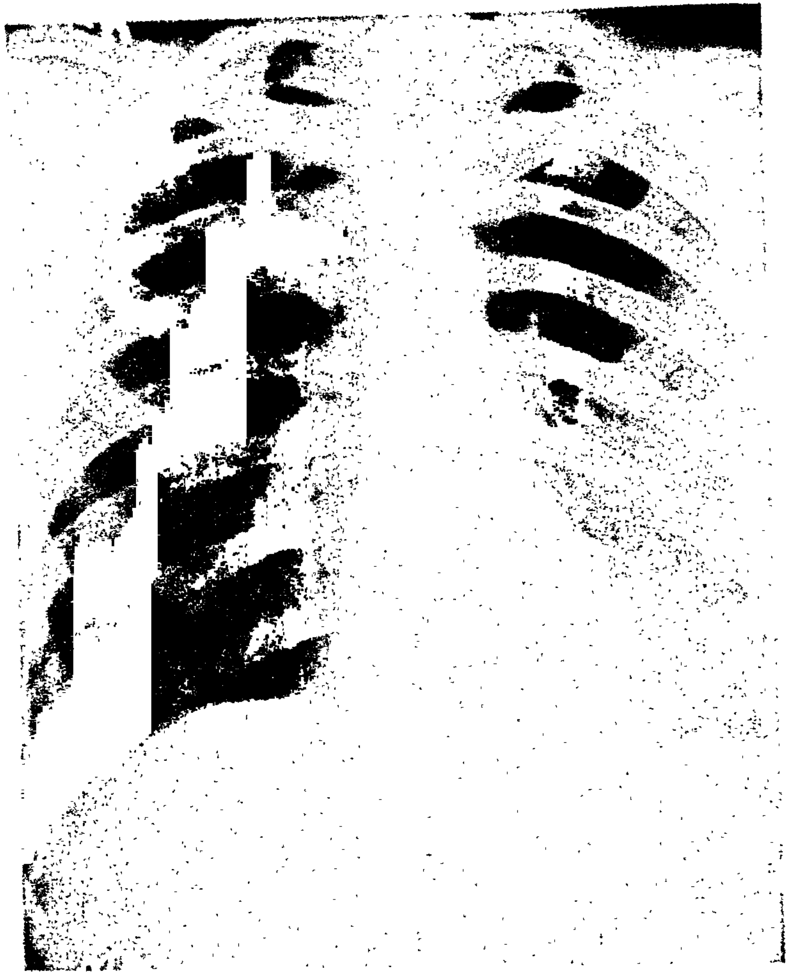

Fig. 2B.

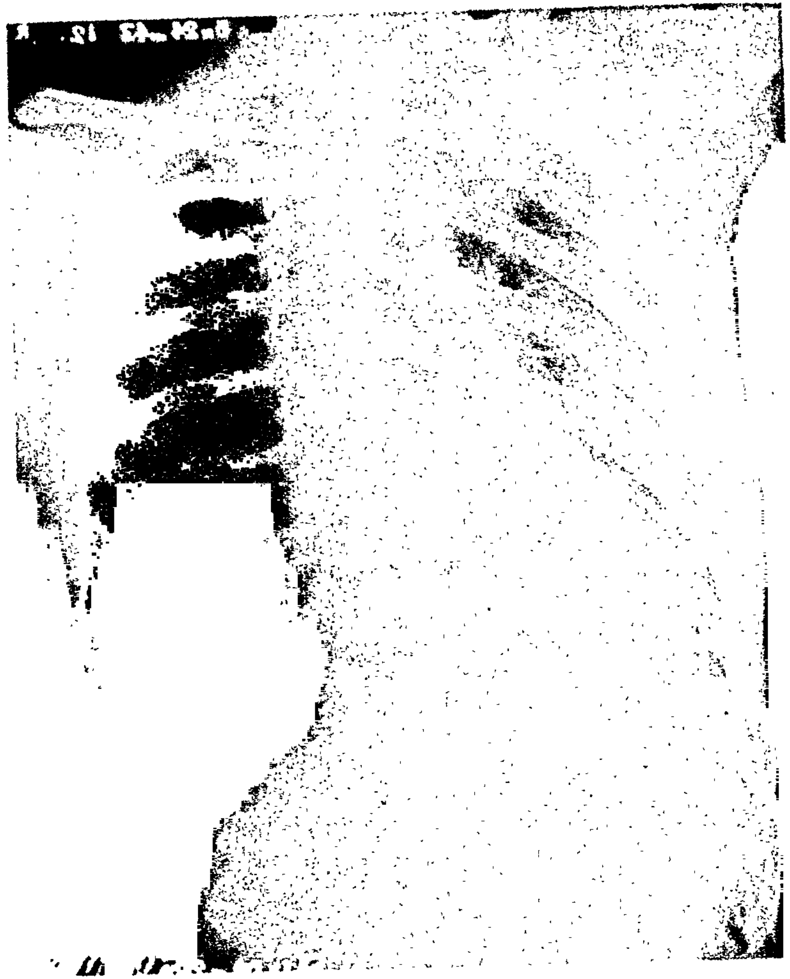

Fig. 2C.

Fig. 2B.—Case 2. Roentgenogram taken after subsidence of the pericardial effusion, showing the bullet in the wall of the left ventricle.

Fig. 2C.—Case 2. Right anterior oblique view showing the bullet in the heart wall.

The metallic foreign body, not discernible in the above reproduction of the film, was visible approximately 2 cm. inside the left border of the cardiac shadow and was seen to move slightly with each systole of the heart. Chemotherapy was resumed, and 650 c.c. of sterile serosanguineous fluid were aspirated from the pleural space. He progressively improved and subsequent x-rays showed a gradual diminution of both the pericardial and the pleural effusions.

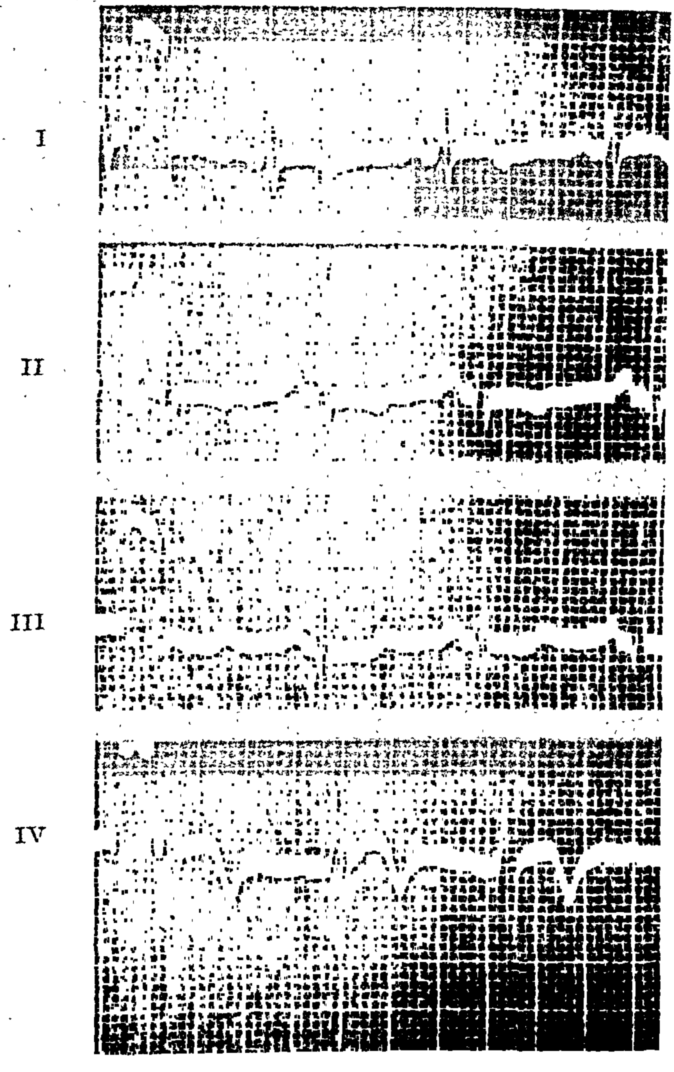

Fig. 3.—Case 2. The electrocardiogram showing inversion of the T waves in Leads I, II, and IV, consistent with myocardial injury in the region of the cardiac apex.

Six weeks after his injury he came for the first time under our observation. By this time his general condition was good, and his only complaints were: (1) dyspnea on effort, (2) a moderately bothersome and slightly productive cough, and (3) a feeling of muscle tightness on deep inspiration at the site of the wound, now well healed. X-ray and fluoroscopy at this time showed that the heart was now normal in shape, size, and pulsations. The foreign body lay within the cardiac shadow in its entirety and was located anteriorly just above the apex of the heart, presumably in the wall of the left ventricle (Figs. 2*B* and 2*C*). It moved inward vigorously with cardiac systole and there was no evidence of aneurysmal bulging of the heart wall in this vicinity. A hydropneumothorax of moderate degree persisted.

An electrocardiogram was characteristic of myocardial injury in the region of the cardiac apex (Fig. 3). It showed a sharp late inversion of the T waves in Leads I, II, and IV, with a slight elevation of the S-T segments in Leads I and IV.

Comment.—Two months after his injury this patient was evacuated to the United States. It appears as though he will make a complete recovery, barring pulmonary complications. The retained foreign body is probably firmly embedded in fibrous tissue without seriously weakening the heart wall. Therefore, the danger of disastrous erosion later seems negligible, especially since the force of each heartbeat is directed away from, rather than against, the retained metal. Here again, as in Case 1, the somewhat delayed appearance of pericardial effusion without serious consequences is of interest.

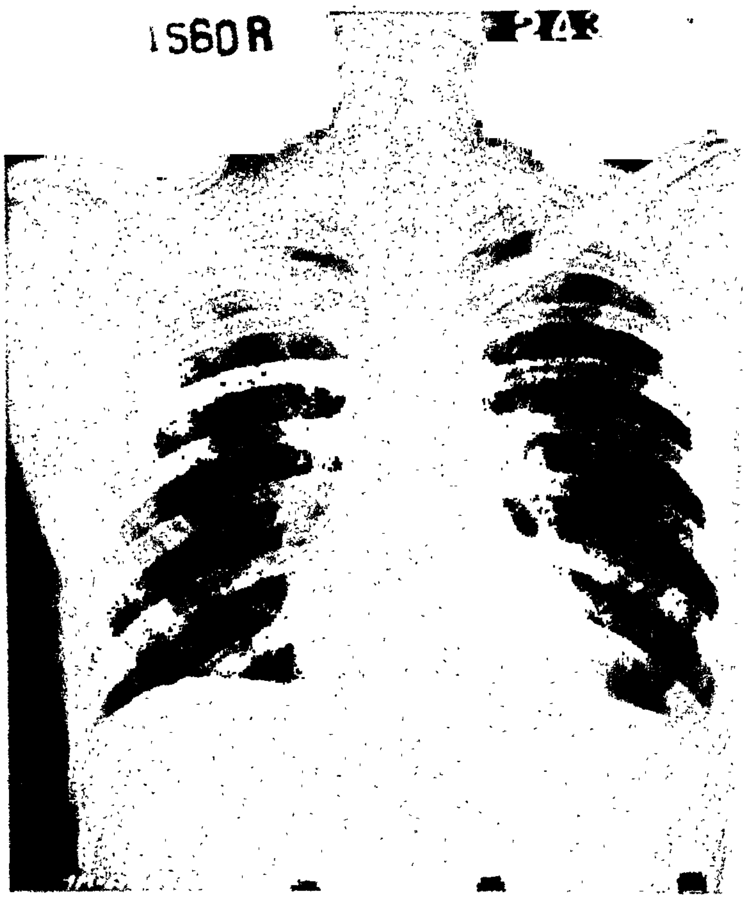

Fig. 4A.—Case 3. Roentgenogram showing a pneumopericardium and a retained foreign body which, in oblique views, lies behind the heart.

CASE 3. *Pneumopericardium With a Foreign Body in the Adjacent Lung.*—A sergeant in the infantry, aged 24 years, was wounded on March 30, 1943, by mortar shell fragments near El Guettar in Tunisia. He received a flesh wound of the left forearm and a perforating wound of the left chest wall in the lower part of the axilla. He immediately experienced severe dyspnea and sharp pain in the left chest on inspiration, radiating upward into the left side of the neck. For about an hour there was a sucking sensation at the site of the chest wound, and he coughed up blood for twenty-four hours. His dyspnea slowly subsided

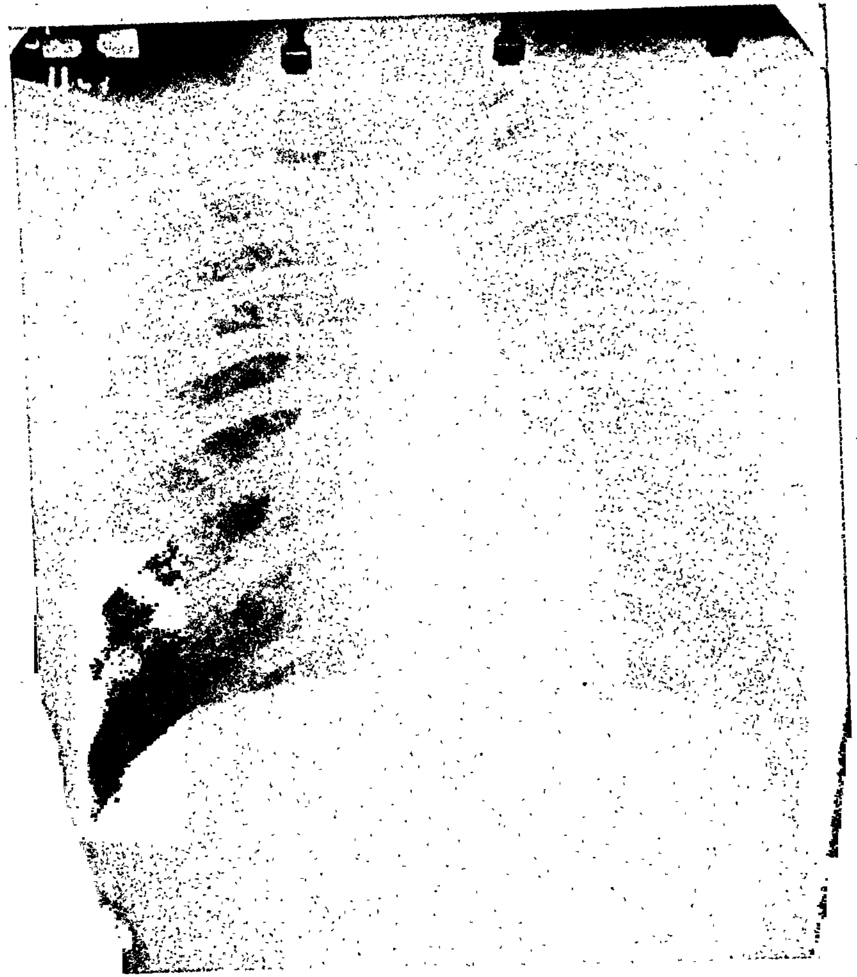

Fig. 4B.

Fig. 4C.

Fig. 4B.—Case 3. Roentgenogram after the pneumopericardium had subsided.
Fig. 4C.—Case 3. A left anterior oblique view showing the foreign body close behind the heart.

in the course of two to three days. No friction rubs were heard and his general condition was good throughout this time. On the third day he was evacuated to a general hospital where the x-ray shown in Fig. 4A was taken. It shows a small metallic foreign body near the heart and a pneumopericardium. The outline of the pericardium is shown by the thin line of density beyond the left border of the heart.

He came under our observation on the tenth day after his injury. He still complained of an occasional sharp stabbing pain along the left border of the heart on deep inspiration, but no friction rub could be elicited. He appeared to be in good condition. The wound of entrance in the left axilla was healing satisfactorily. Examination of his heart and lungs revealed no abnormalities. An electrocardiogram was slightly abnormal in that the T waves were of low voltage in all leads, the greatest amplitude being 1 mm. in Lead I, whereas the voltage of the QRS complexes and the P waves was normal and of good amplitude in all leads.

X-ray examination and fluoroscopy by us at this time showed a 7 mm. rounded foreign body lying about 1 cm. behind the heart near the left auricle (*Figs. 4B* and *4C*). It exhibited no motion with the heartbeat, but there was slight movement with respiration. All evidence of the pneumopericardium had subsided and the left border of the heart now followed the contour previously outlined by the pericardium (compare Fig. 4*A* and Fig. 4*B*).

Comment.—Although he had apparently recovered, he re-entered the hospital three months after his injury, after a trial of light duty, because of intermittent discomfort in the region of the wound of entrance, brought on by effort and aggravated by deep breathing. Because of this, and also because of the greater risk of pulmonary infection from continued sojourn in this theater, he was evacuated to the United States.

CASE 4. *Multiple Fragments of Unusual Origin in the Heart and Lungs.*—A private first class, aged 27 years, came under our observation in July, 1943, with the following history.

In 1936 while hunting rabbits, he was accidentally shot by a friend by a caliber .22 rifle from a distance of about 50 feet. The bullet entered the third intercostal space just to the left of the sternum, penetrated the chest, lodged against and fractured the eighth rib posteriorly on the right side. He was knocked unconscious by the blow, and upon recovery found that he had been taken to a nearby hospital. For several days he raised bloody sputum and had severe pain in the right side of the chest. During the third week the bullet was removed from the chest wall (he has it at home as a souvenir). Thereafter he made a good recovery, but he has a led a quiet life since then because unusual effort causes vague discomfort in the right side of the chest.

In 1938 he spent three weeks in a hospital because of right-sided pleurisy, which was relieved by strapping, but paracentesis was not necessary. Since then he has been bothered by a "catching" pain at the angle of the right scapula on deep inspiration, or upon certain abrupt movements of the trunk. During the Tunisian campaign he had difficulty in keeping up with his company because of an aggravation of the above discomfort and, hence, he was sent to the hospital for study, in July, 1943.

On physical examination he appeared to be in excellent condition and the only positive findings were: (1) a circular scar 1 cm. in diameter in the third interspace just to the left of the body of the sternum, (2)

a small operative scar at the lower angle of the right scapula 1.5 cm. in diameter where the bullet had been removed, and (3) slight irregularity and deep tenderness over the eighth rib in this region. An electrocardiogram was normal.

Fluoroscopy and x-ray films revealed the extraordinary picture of multiple small metallic foreign bodies scattered throughout the right side of the thorax (thirteen were identified) (see Figs. 5*A*, 5*B*, and 5*C*).

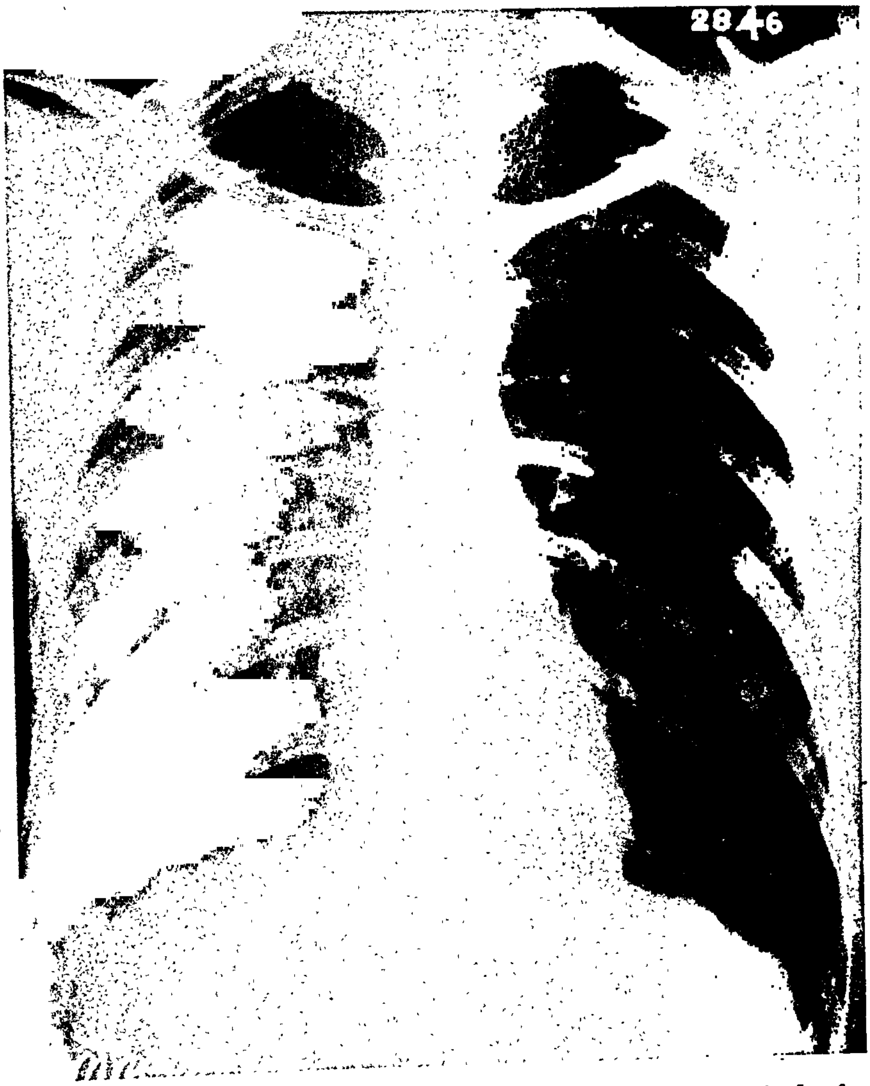

Fig. 5*A*.—Case 4. Roentgenogram showing multiple small foreign body fragments in the right lung and heart wall.

At the site of the now well-healed fracture of the eighth rib in the right posterior axillary line, we localized three fragments measuring up to 4 mm. There was moderate bony overgrowth of the rib in this region and thickening of the adjacent pleura. Also in the right mid-lung field there was a collection of tiny metal fragments with localized fibrosis of the lung in this region. Likewise, at the hilus of the right lung, close to the heart and moving slightly with respirations, we counted four U-shaped fragments measuring up to 4 mm. in their greatest diameter. And finally, in the right anterior oblique view, well shown in Fig. 5*C*, could be seen three additional foreign bodies within the heart shadow in the region of the right auricle. They moved vigorously with each cardiac pulsation. The activity of the lowest of the three was most marked with a range of motion estimated at 1 cm.

Fig. 5B.

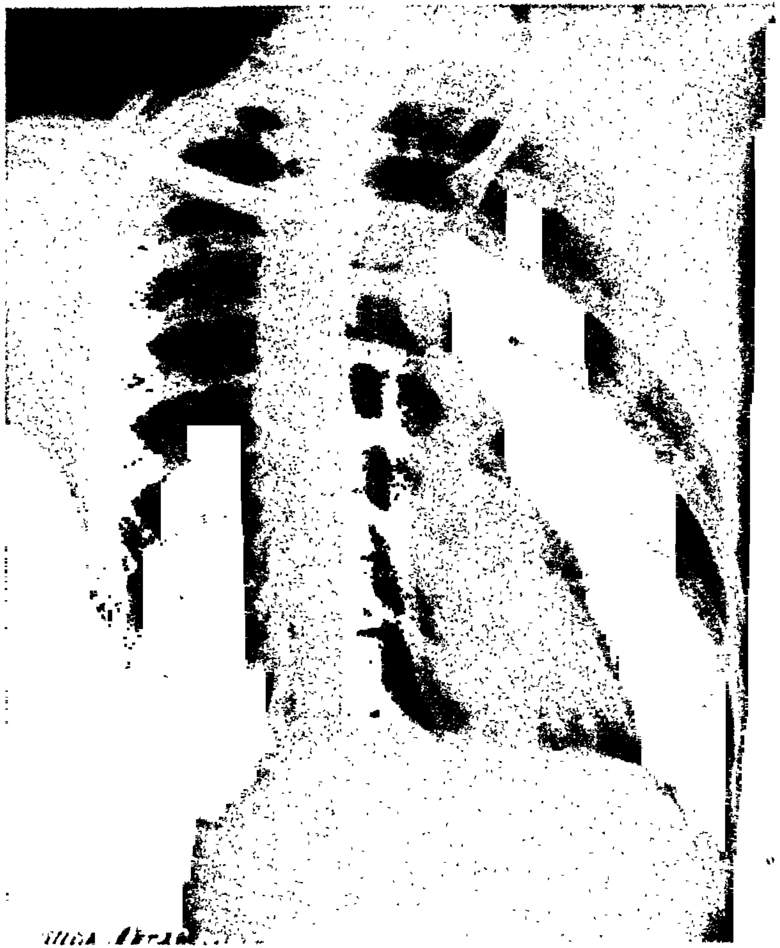

Fig. 5C.

Fig. 5B.—Case 4. A left anterior oblique view showing the peculiar U-shaped contour of some of the fragments.

Fig. 5C.—Case 4. A right anterior oblique view showing three small fragments in the posterior wall of the heart. The U-shaped contour of several is also well seen in this view.

Comment.—At first glance we were puzzled as to the source and nature of these numerous small fragments so widely scattered through the right lung and heart wall, especially since the entire bullet had been removed shortly after his injury seven years before. However, the multiplicity, the uniformly small size, and the peculiar U-shaped appearance of some of these fragments gave us a clue. On requestioning, the patient recalled that on the day of his accident he was wearing a heavy hunting shirt fastened by a 6 inch zipper in front, the position of which corresponded with the point of entrance of the bullet. Unfortunately, the patient never saw his shirt after the accident and nothing was ever said to him as to its damage other than that it was "ruined." It seems, however, that a zipper shattered by the impact of the bullet offers the most likely explanation as to the source of these fragments of metal. His present symptoms are probably due to persistent irritation at the site of the healed fracture. Removal of the retained fragments underlying this rib is probably indicated but, because of other considerations, the patient has been returned to the United States for further study and treatment. There is no indication that the fragments retained in the heart wall or in the substance of the lung have caused serious trouble.

CONCLUDING REMARKS

The favorable course of these four patients, in spite of the temporary complication of pericarditis with effusion in two instances, together with a similar favorable outcome in the remaining four patients in this series, illustrates again the now well-known ability of the heart to withstand physical injury and even to tolerate sizable slugs of metal within, and adjacent to, its walls.

It is our plan to follow the subsequent course of these patients to determine if later ill effects result from the retained metallic bodies. The available data suggest a relatively uncomplicated future, as illustrated by Case 4, and also by an additional patient in this series (Case 5), not reported in detail here, who was shot accidentally in 1925 by a caliber .38 revolver. The retained bullet lies directly against the ascending aorta, moving vigorously with each pulsation. During the ensuing eighteen years this patient has attained some renown as a prize fighter and has had no symptoms related to the intrathoracic bullet.

In the remaining three patients of the series there have been no serious complications, and the foreign bodies are located as follows:

CASE 6.—There are two fragments in the heart muscle, one of which lies anteriorly in the region of the aortic orifice and moves violently with each heart beat; the second lies posteriorly in the cardiac wall near the junction of the left auricle and ventricle. The electrocardiogram shows late inversion of the T waves in all four leads.

CASE 7.—There is a jagged metallic fragment measuring 2 by 0.5 cm. at the lower anterior border of the heart in the region of the right ventricle. The electrocardiogram is normal.

CASE 8.—In the right posterior aspect of the heart, probably in the wall of the right auricle, or in the pericardial tissue, there is a 7 mm. fragment of metal which moves so vigorously with each heartbeat that it is photographed with difficulty. The electrocardiogram is normal.

SUMMARY

The case histories of four patients (from a series of eight) with penetrating chest wounds and retained foreign bodies in, or adjacent to, the heart are recorded. Pericardial effusion was a complicating feature of two, pneumopericardium of one, and the fourth case was included because of the unusual origin of the retained metal fragments, namely, a shattered zipper. The available evidence suggests that the later course of these patients will be favorable.

I am indebted to Lt. Col. James R. Lingley and Capt. Stanley M. Wyman of the X-ray Department for their interest and expert aid in localizing the foreign bodies recorded in this report, and to the Signal Corps for the illustrations.

THE CARDIOVASCULAR SYSTEM IN TRAUMATIC SHOCK

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INVESTIGATIONS on secondary or traumatic shock were first undertaken on a large scale as a result of the importance which this problem assumed during World War I. A large body of clinical and experimental observations were recorded then and well summarized in the monograph by Cannon,[1] published in 1923. Moreover, during the interval between the war, 1914 to 1918, and the outbreak of the present conflict, a voluminous literature on shock has appeared. Study of this material permits the formation of a reasonably clear picture of the fundamental cardiovascular disturbance, the chain of events leading to death, and the relative importance of various possible initiating factors. The following discussion will be limited to a consideration of studies in this field which already have been published, and, for obvious reasons, no reference will be made to any of the very extensive and confidential investigative programs which are at present in progress on many aspects of the shock problem.

The best short definition of shock is that of Harkins,[2] "a progressive, vasoconstrictive, oligemic anoxia." Most of the essential elements of its pathologic physiology are implicit in this definition, and these can be most readily amplified and illustrated by resorting to a diagrammatic representation (Fig. 1), for many features of which we are indebted to Blalock,[3] McDowall,[4] Moon,[5] and Freeman.[6]

The bracketed phases of this diagram constitute the fundamental hemodynamic disturbances of traumatic shock and account fully for its specific clinical features. It is essential to differentiate between these primary circulatory factors and the nonspecific environmental and functional alterations in the tissues, which result from reduction in blood flow, and which lead to a fatal outcome when occurring in the vital organs. It is also important to emphasize that this potential cycle of shock may be initiated at any one or more of its several constituent stages, and that only factors which act in this way can be of etiological significance.

The following discussion will be concerned first with the relatively well-established specific circulatory changes that occur in shock, and

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This paper was written in connection with studies made under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Massachusetts General Hospital.

This is reprint No. 584 of the Cancer Commission of Harvard University.

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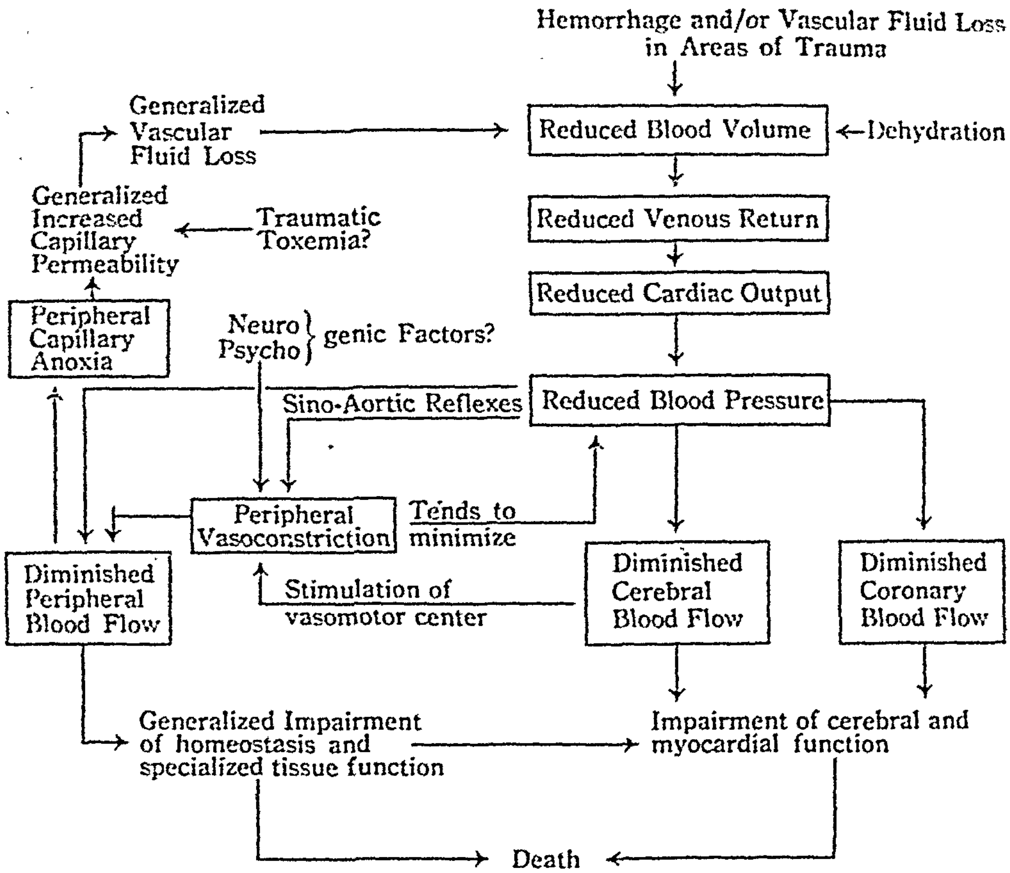
Fig. 1



their consequences to the economy of the organism. There will follow a brief consideration of more controversial matters, including the problem of etiological factors and that of the state of "irreversible" shock.

FUNDAMENTAL HEMODYNAMIC DISTURBANCE

Whatever may be their differences on other aspects of the problem, all who have studied traumatic shock in recent years are in substantial agreement upon the disturbances in cardiovascular function which characterize it. These may be expressed as a sequence of events resulting from reduction in blood volume and leading in turn to diminution in venous return, reduction in cardiac output, reduction in blood pressure, and consequent decrease in blood flow to vital centers. Each step in this sequence not only is reasonable on purely theoretical grounds, but also is substantiated by measurements in experimental animals, and many of the cardiovascular derangements are being corroborated by studies on traumatic shock in man. Noteworthy are the extensive clinical investigations carried on at the Bellevue Hospital in New York,[7] to which we shall have occasion frequently to refer.

All the evidence indicates that a reduction in effective blood volume is of fundamental importance. Recently, it has been emphasized that some of this reduction may represent blood which is trapped in occluded vascular beds;[4-16] but, nevertheless, such sequestered blood is

effectively lost to the circulation. In severe traumatic shock in man the average reduction in blood volume has been found to approximate 40 per cent.[7]

The early and marked reduction in right auricular pressure which is constantly found in all types of shock[7, 11-13] is reasonable evidence of a significant reduction in venous return, upon which undoubtedly depends the severe diminution in stroke volume[7] and cardiac output per minute.[7, 11, 14, 15] The contrast between this mechanism by which the cardiac output is reduced, and primary myocardial failure is obvious.

The reduction in cardiac output is the precursor of the fall in blood pressure which has classically characterized the shock syndrome, although as a result of certain compensatory changes the earlier disturbances may progress considerably before a significant hypotension occurs. Since the maximal flow of blood through the cerebral and coronary vessels is limited by the intra-arterial pressure, this fall in blood pressure assumes grave significance.

By invoking certain compensatory mechanisms, however, the organism is enabled to survive a reduction in effective blood volume which would otherwise lead rapidly to death. There is evidence that moderate blood loss is not followed by a significant decrease in cardiac output,[16] which may indicate a certain blood volume reserve brought into play by venous constriction. A fall in blood pressure, through diminution of the inhibitory impulses from pressure receptors in the carotid sinus and aortic arch,[17] causes an increase in cardiac rate and, augmented possibly by direct stimulation of the vasomotor center through severe decreases in cerebral blood flow,[18] produces a generalized peripheral arteriolar constriction. In this, the cerebral and coronary vessels take little part because of their relatively ineffectual constrictor innervations,[19-21] and the net effect is a redistribution of the diminishing output of the heart toward the brain and myocardium at the cost of a great reduction in blood flow through less essential vascular beds such as those of the skin, gastrointestinal tract, kidneys, and muscle.[22] Although an increase in the total peripheral resistance[59] and diminished circulation in certain regions have been demonstrated experimentally,[23-25] the only measurements in clinical shock (complicated unfortunately by alcoholism) show reduction in total peripheral resistance.[7]

The rate and depth of respiration are increased as a result of both direct and reflex stimulation of the respiratory center,[17, 18, 20] and these respiratory changes persist throughout all but the terminal stages of shock. They occur before there is a significant change in arterial carbon dioxide tension or pH, and one of the results may be to augment venous return through exaggerated fluctuations in intrathoracic pressure.

The combination of diminished arterial pressure and generalized arteriolar constriction results in a considerable fall in the effective capillary filtration pressure. Mobilization of extravascular fluid is thus achieved, and the first step in the restoration of plasma volume is

initiated. If the organism is able to survive the early effects of blood or plasma loss, regeneration of plasma protein and cellular elements occurs to complete the restitution.

There has been unwarranted emphasis on arterial or venous hematocrit values as an index of plasma loss or gain. A layer of relatively stagnant plasma adjacent to vessel walls, which is of appreciable magnitude in the smaller vessels, has been demonstrated.[26] This makes the erythrocyte concentration in capillary blood considerably lower, and, in great vessel blood, higher, than the average body hematocrit. Furthermore, since this plasma layer varies in magnitude according to the total capillary surface and velocity of blood flow, changes in these factors may cause misleading changes in the hematocrit values of blood taken from peripheral veins.[27] Such effects as these may explain the inconsistent results of hematocrit determinations in various types of shock. Although hemorrhagic shock has usually been thought to be associated with hemodilution and traumatic shock with hemoconcentration on the basis of hematocrit studies, one group has recently reported[7] consistently reduced red cell hematocrits in cases of shock from skeletal trauma without evidence of gross hemorrhage.

From these fundamental disturbances stem all the clinical manifestations which have long been recognized as characteristic of shock. The feeble pulse and low pulse pressure are reflections of the diminished stroke volume and increased peripheral resistance. The tachycardia and hyperpnea arise from reflex and central mechanisms already discussed, while the pallor, clammy skin, and cold extremities are manifestations of generalized sympathetic activity and diminished peripheral blood flow. Mental indifference, drowsiness, or stupor are undoubtedly signs of a severely depressed cerebral blood flow.

IMPAIRMENT OF HOMEOSTASIS AND MECHANISM OF DEATH

The foregoing discussion has shown that the most serious consequence of primary reduction of blood volume is a diminished blood flow to the brain and heart and to the peripheral tissues. It has also been emphasized that the relative ischemia of the latter is greater than that of the former because of the additive effects of peripheral vasoconstriction and reduction of blood pressure. Indeed, compensatory reactions may maintain the blood pressure at normal levels so that cerebral and coronary blood flow is unaffected, but only at the expense of a greatly diminished peripheral flow.

The normal circulation of blood is by far the most important factor in the maintenance of the homeostasis of the tissues. Homeostasis is the term used by Cannon[28] to denote his far-reaching concept that the complex functional activities of all specialized organs and tissues of multicellular animals are directed toward the maintenance of constancy in the chemical and physical environment of all cells, similar to that in the seas in which living processes had their origin. Diminution

of blood flow to a tissue will, therefore, be followed by a serious disruption of homeostasis. Not only is there a reduction of the delivery of oxygen, oxidizable substrates, and other nutrients, but there is impairment in the removal of carbon dioxide and nitrogenous and acid end products of tissue metabolism. Sufficient lowering of the oxygen tension will result in interference with oxidative reactions, and owing to the consequent block in terminal oxidations, fermentative breakdown of carbohydrates undoubtedly tends to become predominant. An important and harmful consequence of these changes is the production of acidosis[29, 30] due to the accumulation of lactic[31] and other fixed acids in the blood stream. All of these metabolic and environmental abnormalities eventually lead to interference with the specific functional activities of the tissues. Breakdown of the integrity of cell membranes releases intracellular constituents, which may appear in high concentration in the blood as in the case of creatine[32] and potassium.[33] Capillary anoxemia, if prolonged, may result in increased permeability and perpetuation of the shock cycle, as will be discussed in connection with the problem of irreversible shock.

Although the degree of ischemia is less marked than in the peripheral tissues, losses of functional integrity eventually occur in the heart[34] and in the central nervous system, and in these organs such changes lead directly to death, which is usually the result of respiratory failure.

INITIATING FACTORS

The most controversial aspect of the shock problem concerns the mode by which the characteristic progression of changes is initiated. Theoretically, reduction in blood volume can be brought about by any factor that sets in motion the potential vicious cycle. In clinical shock such factors could include primary vascular fluid loss, intense neuropsychogenic stimulation, and the action of hypothetical toxins derived from traumatized tissue. Experimentally, shock can be produced in any of these ways, but great caution is necessary in the interpretation of the results of such experiments, and much confusion has arisen from the conclusion that because a given factor could initiate this progression of events, it must, therefore, be of etiological significance in clinical shock.

It is self-evident that gross uncomplicated hemorrhage can induce these changes, and the important work of Blalock,[35-37] of Parsons and Phemister,[38] and of others has clearly shown that the local fluid loss in traumatized areas is entirely sufficient to account for the shock that develops under the conditions of their experiments. There is now rather general agreement that primary vascular fluid loss at the site of injury is by far the most important factor in the genesis of subsequent shock. In this connection it is of some interest to quote from an excellent clinical study of actual battle casualties in England during the present war, by Keckwick, Marriott, Maycock, and Whitby,[39] "In all cases of trau-

matic shock seen by us it has appeared that the loss of blood volume can be accounted for by external loss and by extravasation into the injured area. In no case has there been any evidence to suggest a loss of plasma in regions remote from a seat of injury."

The theory of traumatic toxemia postulates the elaboration of a toxic factor in damaged tissues which is absorbed into the circulation and has a generalized action in bringing about a reduction in blood volume and hemoconcentration, either by causing peripheral stagnation and pooling of the blood in dilated venous or atonic capillary beds, or by producing a primary generalized increase in capillary permeability.

The toxic theory of shock is based upon two types of experimental evidence. In one, shock is produced in animals by the parenteral administration of various extracts of normal and traumatized tissues.[4, 40] In the other, attempts are made, either by cross-circulation or cross-transfusion experiments of varying degrees of complexity,[41-43] or by measurement or control of local fluid loss,[44-48] to show that some factor other than fluid loss is necessary to explain the production of shock in animals subjected to various forms of trauma. Experiments of the first type are not always consistently positive, especially when the element of bacterial contamination is controlled,[49] and at best they furnish only indirect evidence for the activity of toxic substances derived from traumatized tissues. Careful scrutiny of experiments of the second type reveals that in every case either other factors have not been adequately controlled, or traumatic fluid loss is sufficient to explain the results.*

The neurogenic theory of the etiology of shock depends upon the assumption that either there is sequestration of blood in postarteriolar vascular beds, or that prolonged severe vasoconstriction will result eventually in capillary leakage and hence reduction in blood volume. That the latter can occur experimentally has been shown by the work of Freeman,[50] and clinical experience has indicated that nervous and psychic factors may hasten or accentuate the development of shock in wounded individuals. There is, moreover, considerable experimental evidence[6, 10, 24, 51, 52] which appears to support this theory. However, in most laboratory experiments neurogenic factors are controlled by the use of barbiturate anesthesia, and both the neurogenic and toxic theories are rendered open to serious question by the inability of investigators to find evidence for an increase in capillary permeability in either clinical[7, 29] or experimental shock.[53] Moreover, many experiments have shown that when fluid loss in traumatized regions is prevented, shock fails to develop.[54-56]

It seems reasonable, therefore, to state that hemorrhage and traumatic effusion each has been demonstrated to be a necessary and sufficient cause for the development of shock, and that while other factors (neurogenic, toxic) have not been shown to be necessary causes, they

*A critical analysis of experimental studies bearing on the toxic theory of shock will be included in a future publication.

are sufficient ones under certain experimental conditions and have not been excluded as playing at least a contributory role in the genesis of both experimental and clinical shock.

THE PROBLEM OF IRREVERSIBLE SHOCK

It is possible with care and, when necessary, by removal or transfusion of appropriate amounts of blood, to maintain an animal in a state of severe hypotension with arterial blood pressures of about 30 to 40 mm. for a period of several hours. If the circulatory embarrassment has been sufficiently severe and prolonged, a state is reached in which even the reinjection of all blood removed will result in no improvement, and death cannot be prevented. Post-mortem examination of such animals usually reveals hemorrhage into the gastrointestinal tract and visceral congestion.[34, 57] Until recently, a satisfactory explanation for this irreversible state lay in the supposition that intense peripheral vasoconstriction, by virtue of the capillary blood stagnation and anoxemia, so damaged the endothelium as to render it permeable to blood colloids and cellular elements. That such a chain of events is possible is indicated by the experiments of Freeman and collaborators[50] who were able to produce fatal shock with demonstrable gastrointestinal hemorrhage by the continuous intravenous administration of epinephrine. Landis[58] has shown that capillary stagnation and anoxia may result in abnormal endothelial permeability. Fine and Seligman[9] found evidence of loss of tagged plasma protein into some organs in the last stages of hemorrhagic shock. The bulk of evidence indicates, however, that generalized loss of plasma proteins either does not occur,[7, 8, 39] or if it occurs, is insufficient to explain the state of irreversibility.[9, 34] Two other mechanisms have been offered as possible explanations for this puzzling phase of shock: a pooling of blood in the postarteriolar vascular bed,[8] and myocardial failure.[34, 59] Further studies are necessary before their relative roles can be evaluated.

Irreversibility is apparently an important cause of therapeutic failures in cases of human shock,[60] and elucidation of its pathologic physiology is, therefore, imperative.

The authors wish to express their great indebtedness to Drs. Joseph C. Aub, Austin M. Brues, Ira T. Nathanson, and Paul C. Zamecnik for invaluable suggestions and criticisms in connection with the preparation of the foregoing discussion.

References to the literature on traumatic shock are necessarily limited to certain articles especially pertinent to the present discussion. Extensive and complete bibliographies on shock are available in the excellent reviews of Harkins[2] and Wiggers.[34]

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American Heart Journal

VOL. 27 MAY, 1944 No. 5

Original Communications

EFFECT OF EXTERNAL HEAT AND COLD ON PATIENTS WITH ANGINA PECTORIS: EVIDENCE FOR THE EXISTENCE OF A REFLEX FACTOR

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INTRODUCTION

PATIENTS with angina pectoris commonly experience an increased frequency of attacks during cold weather. This clinical observation has been corroborated by recent laboratory studies[1] which showed that almost all patients with angina pectoris experience typical attacks during exercise in a cold room (45 to 55° F.), whereas many patients fail to develop angina with similar or more severe exercise at ordinary room temperatures (72 to 75° F.). The standardized exercise tolerance test[1] for angina pectoris is based on this phenomenon. To gain insight into the mechanisms responsible for variations in the severity of angina pectoris under different thermal conditions, studies have been made of the effects of general and local application of heat and cold on the exercise tolerance of patients with angina pectoris. Experiments bearing on the mechanisms of the changes observed have also been performed.

MATERIAL AND METHODS

Twenty-two patients with angina pectoris due to coronary arteriosclerosis were studied; twenty were men. All had been observed over periods ranging from months to years in a special clinic devoted to the study of angina pectoris; the amount of exercise under standardized conditions necessary to produce attacks of angina pectoris had been measured in each case on many occasions, and the tests were in satisfactory agreement.

The standardized conditions of the test were similar to those described previously:[1] The patient repeatedly mounted and descended a two-step staircase in a room (cold room) which was kept at a temperature of 45 to 55° F. until he was forced to stop by a typical attack of angina.

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Received for publication May 13, 1943.

All tests were carried out at least one hour after a light breakfast and after the patient had rested a minimum of one-half hour. Only one test was carried out on any one day, and all measurements of the effects of a given procedure were made on at least two occasions. The patient received no medication during the period of study. Under these conditions, the amount of work necessary to precipitate angina in most cases was extraordinarily constant, varying within plus or minus 10 per cent of the patient's average exercise tolerance.

To observe the effect of heat, tests were carried out under the following conditions: (a) the patient exercised at temperatures of 72 to 75° F. (warm room): (b) on another day he repeated the exercise tolerance test in the cold room after he had immersed his hands and wrists in water at 110° F. for ten minutes or applied a chemically heated pad* at a temperature of 110° F. to the bare skin, usually of the abdomen, for ten minutes.

To observe the effect of locally applied cold, the patient exercised at room temperatures of 72 to 75° F. while holding an ice cube in one hand. In a few instances the local effect of cold was obtained by strapping ice to the thigh or by spraying ethyl chloride upon the exposed back.

Electrocardiographic studies, utilizing Lead IVR, were carried out during exercise in the manner previously described.[2, 3] Tracings were obtained with the patient at rest, immediately before cessation of exercise and continuing for fifteen seconds thereafter, and one, three, and five minutes later. The change in the initial portion of the S-T segment, as compared with the terminal portion of the P-R interval, was measured. The changes in ten consecutive complexes were measured and averaged.

RESULTS

I. THE EFFECT OF HEAT AND COLD ON THE EXERCISE TOLERANCE OF PATIENTS WITH ANGINA PECTORIS

The Effects of Varying the Temperature of the Environment on the Exercise Tolerance.—When the test was carried out at a room temperature of 72 to 75° F., 12 of the 22 patients were able to do considerably more work than was possible in the cold room (45 to 55° F.) (Table I). The average exercise tolerance of these 12 patients was 52.5 trips at ordinary room temperature, as compared with 37.2 trips at 45 to 55° F.; 7 of the 12 patients failed to develop pain when they exercised at ordinary room temperature (72 to 75° F.). In 10 cases the exercise tolerance was not affected by the environmental temperature; the average exercise tolerance was 27.5 trips at ordinary room temperature and 30.6 trips in the cold room (Table I).

The Effect of Local Application of Heat on the Exercise Tolerance.—This study was made on 19 patients after the exercise tolerance was established in the cold room. Eleven of the 19 patients (Table I) were able to do more work when, after immersion of the hands and wrists in hot water, the test was repeated in the cold room. The average exercise tolerance was 52.4 trips in the cold room after immersion of the

*The chemically heated pads (Thermat) used in this study were supplied by Becton, Dickinson, & Co.

hands and wrists in hot water, and 35.6 trips in the cold room without such application of heat. Six of the 11 patients (Table I), however, stopped exercising because of fatigue, without developing pain. The increase in exercise tolerance was approximately the same after immersion of the hands and wrists in hot water and after application of a chemically heated pad to the abdomen. Immersion of the hands and wrists in hot water before entering the cold room enabled 9 of these 11 patients to do essentially the same amount of work in the cold as they were able to do at ordinary room temperature (Table I).

In 8 cases, immersion of the hands and wrists in hot water was without significant effect; the exercise tolerance averaged 32.9 trips after the application of heat and 29.6 trips without previous application of heat (Table I).

TABLE I

EXERCISE TOLERANCE

	NUMBER OF TRIPS OVER TWO-STEP STAIRCASE				
	ROOM TEMPERATURE 45 TO 50° F.			ROOM TEMPERATURE 72 TO 75° F.	
PATIENT	NO MEDICATION	TWO MINUTES AFTER 1/200 gr. NITROGLYCERIN	AFTER IMMERSING HANDS IN HOT WATER (110° F.) FOR TEN MINUTES	NO MEDICATION	PATIENT HOLDING ICE CUBE
H. Schr.	26	50+*	50+	53+	34
H. C.	17	30+	30+	25+	22
S. W.	28	45+	45+	40+	29
R. S.	22	44+	41	31+	23
V. B.	29	40+	40+	40+	30
H. Schl.	54	62+		62+	43
H. B.	78	100+	100+	100+	92
L. W.	36	76	58	69	39
S. R.	50	75+	65	67	47
S. L.	26	39	36+	38	29
P. R.	44	62+	54	59	39
M. L.	36	60+	57	46	35
H. S.	61	67	67	63	63
B. A.	50	50	50	52	50
B. K.	30	26	33	28	28
S. E.	27	27	27	25	27
M. A.	24	28	24	25	23
F. G.	23	22	28	25	25
B. S.	18	19	22	19	17
R. B.	13	13		16	15
L. B.	10	9		12	12
J. G.	5	10	12	10	5

*+ = Patient stopped exercise because of fatigue or upon request.

Comparison of the Effect of Heat With the Effect of Nitroglycerin.— In all of the 22 cases the effect on exercise tolerance of the prior application of heat was essentially the same as the effect of the sublingual administration of 1/200 grain of nitroglycerin two minutes before the beginning of exercise (Table I). Thus, the twelve patients who were able to do more work at ordinary room temperature or in the cold after

the local application of heat also showed an increase in exercise tolerance after the administration of nitroglycerin. In 3 of these cases the amount of exercise performed in the cold room without pain was appreciably greater with nitroglycerin than the amount of exercise which the same persons were able to do in a warm atmosphere or in the cold after immersion of the hands and wrists in hot water (Table I).

The remaining ten patients were able to do no more work (Table I) in a warm room or in the cold room after the administration of nitroglycerin or the local application of heat than under the standard conditions in the cold room (45 to 55° F.).

The Effect of Locally Applied Cold.—Twenty-one of the 22 patients invariably had attacks of angina pectoris with exercise at ordinary room temperature when they held an ice cube in one hand. In the few instances studied, strapping ice to the thigh or spraying ethyl chloride upon the exposed back gave the same results. The attacks were identical with those experienced in daily life and with those produced by the standardized exercise tolerance test in the cold room. The exercise tolerance in a warm room while holding an ice cube was similar to that under the standardized conditions in the cold room in nineteen of the 22 cases (Table I). Of the remaining three patients, two performed 8 and 14 trips more, respectively, and one 11 trips less, than when exercising in the cold room.

The Time Necessary to Obtain the Effects of Local Chilling.—This was studied in 3 cases (Fig. 1). There was an appreciable reduction in the exercise tolerance, although the patient discarded the ice cube ten seconds after the onset of exercise. The maximum effect of locally applied cold in decreasing the exercise tolerance was observed on two patients who held the ice for thirty to forty seconds after the onset of exercise.

The Duration of the Effect of Exposure to Generalized Cold.—This was observed in 7 cases. Four patients showed an increase in exercise tolerance of 42 per cent at ordinary room temperatures, as compared

TABLE II

EXERCISE TOLERANCE

	NUMBER OF TRIPS OVER STAIRCASE		
PATIENT	ROOM TEMPERATURE 45 TO 50° F.	ROOM TEMPERATURE 72 TO 75° F.	ROOM TEMPERATURE OF 72 TO 75° F. AFTER EXPOSURE TO ROOM TEMPERATURE OF 45 TO 50° F. FOR THREE MINUTES
H. Schr.	26	53+	38
S. W.	28	40+	28
Y. B.	29	40+	29
H. Schl.	54	62+	51
L. W.	36	60	53
P. R.	44	59	44
M. L.	36	46	27

to the cold; rest for three minutes in the cold room before exercising at ordinary room temperature prevented this increase. The remaining three patients, who rested in the cold room for three minutes and then exercised at ordinary room temperature (72 to 75° F.), were able to do 40 per cent more work than in the cold (Table II); they could do 76 per cent more work in the warm room when not exposed previously to cold.

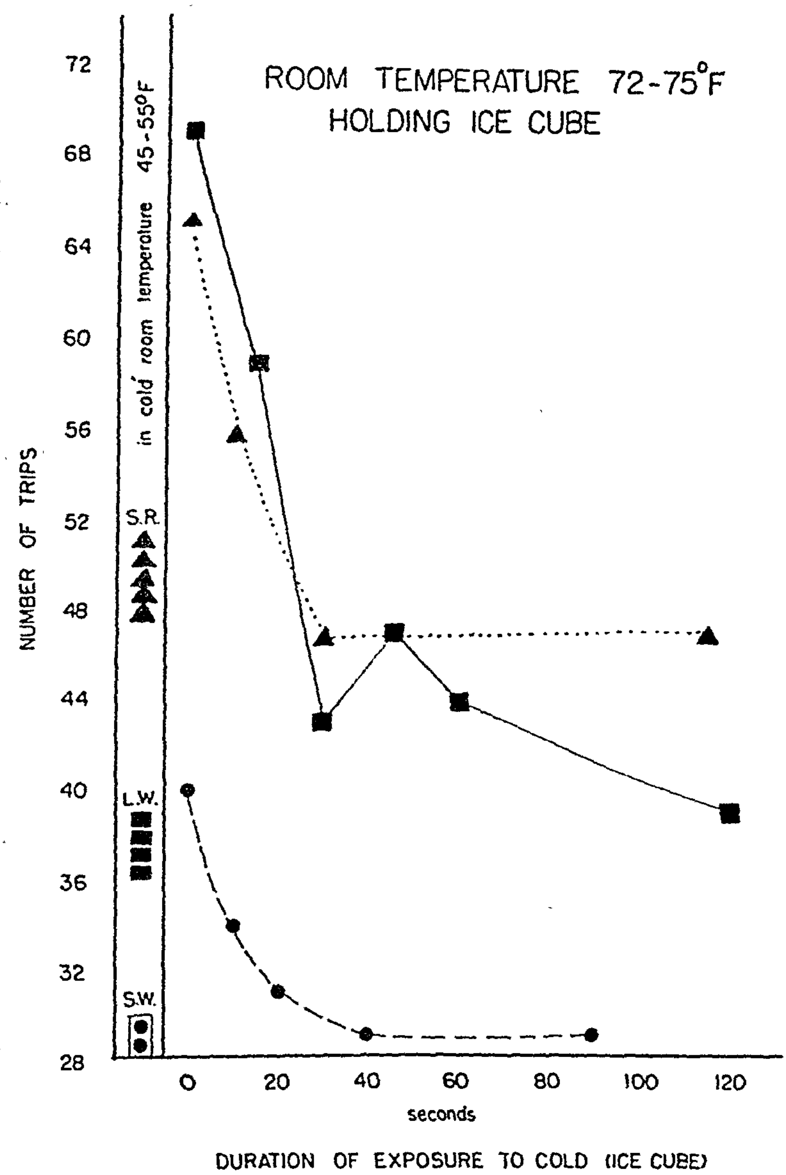

Fig. 1.

II. STUDIES ON THE MECHANISM OF THE EFFECT OF TEMPERATURE ON THE EXERCISE TOLERANCE OF PATIENTS WITH ANGINA PECTORIS

Blood Pressure and Heart Rate.—The effect of local chilling on the arterial blood pressure was studied on five patients with angina pectoris and normal blood pressure. Measurements were made by the auscultatory method every fifteen seconds for two and one-half minutes after the patient, seated at rest, grasped an ice cube in his right hand. No change in blood pressure occurred in four patients, two of whom had

responded to the local and general application of heat by an increase in exercise tolerance. In the fifth case (M. L.), in which warmth or nitroglycerin caused a slight increase in exercise tolerance, the blood pressure increased from 140/80 to 160/94 within fifteen seconds after applying the ice cube, and reached a maximum of 180/100 in two minutes.

Measurements of the blood pressure by the palpatory method and of the heart rate from continuous electrocardiographic tracings during exercise showed no consistent differences when the same amount of exercise was performed in the cold room, in the warm room, in the warm room while grasping an ice cube, or in the cold room after both hands and wrists had been immersed in hot water. In accord with previous observations,[4] the heart rate increased to a greater or lesser degree during exertion, and returned to normal after intervals which, although they varied in different cases, were remarkably constant for each individual. The blood pressure rose or fell during exercise, but invariably rose after cessation of exertion.

Chilling of the Blood Consequent to Local Application of Cold.—In two cases, the venous circulation in the arm holding the ice cube was occluded by a blood pressure cuff which was inflated to about diastolic blood pressure. Angina was induced in each instance by the same amount of exercise as was necessary without the cuff (Table III).

TABLE III

THE EFFECT OF OBLITERATING THE VENOUS RETURN ON THE EXERCISE TOLERANCE

	NUMBER OF TRIPS AT ROOM TEMPERATURE		
PATIENT	NO MEDICATION	NO MEDICATION ICE IN HAND	NO MEDICATION. ICE IN HAND. VENOUS RETURN OBLITERATED BY BLOOD PRESSURE CUFF INFLATED ABOVE DIASTOLIC PRESSURE
S. R.	67	47	48
M. L.	46	35	34

The Effect of Atropine.—Atropine sulfate (1/60 to 1/30 grain) was administered subcutaneously to four patients, and caused no change in the exercise tolerance of two of them under standardized cold conditions; the other two had decreases of 27 and 25 per cent, respectively, under these conditions (Table IV). The oral administration of 1/50 grain of atropine sulfate to three patients failed to produce any change in the exercise tolerance when the work was carried out at ordinary room temperature with an ice cube in one hand.

Electrocardiographic Studies.—Five patients who showed increases in exercise tolerance in response to heat or nitroglycerin and one patient (B.A.) who did not respond to these measures revealed changes in the S-T segment during exercise which were essentially the same, regardless of the temperature of the environment. Three patients who re-

TABLE IV

THE EFFECT OF ATROPINE ON THE EXERCISE TOLERANCE

PATIENT	NUMBER OF TRIPS NO MEDICATION	NUMBER OF TRIPS AFTER ATROPINE
Group A. Exercise Tolerance Studied Under Standardized Conditions. Room Temperature 45 to 50° F.*		
E. S.	20	21
L. S.	20	21
E. W.	38	28
P. R.	44	33
Group B.† Exercise Tolerance Studied at Room Temperature of 72 to 75° F. Patient Holding Ice Cube During Exercise.		
H. Schr.	34	34
L. W.	40	39
S. R.	47	47

*Atropine Sulfate, 1/30 to 1/60 grain subcutaneously.
†Atropine Sulfate, 1/50 grain orally.

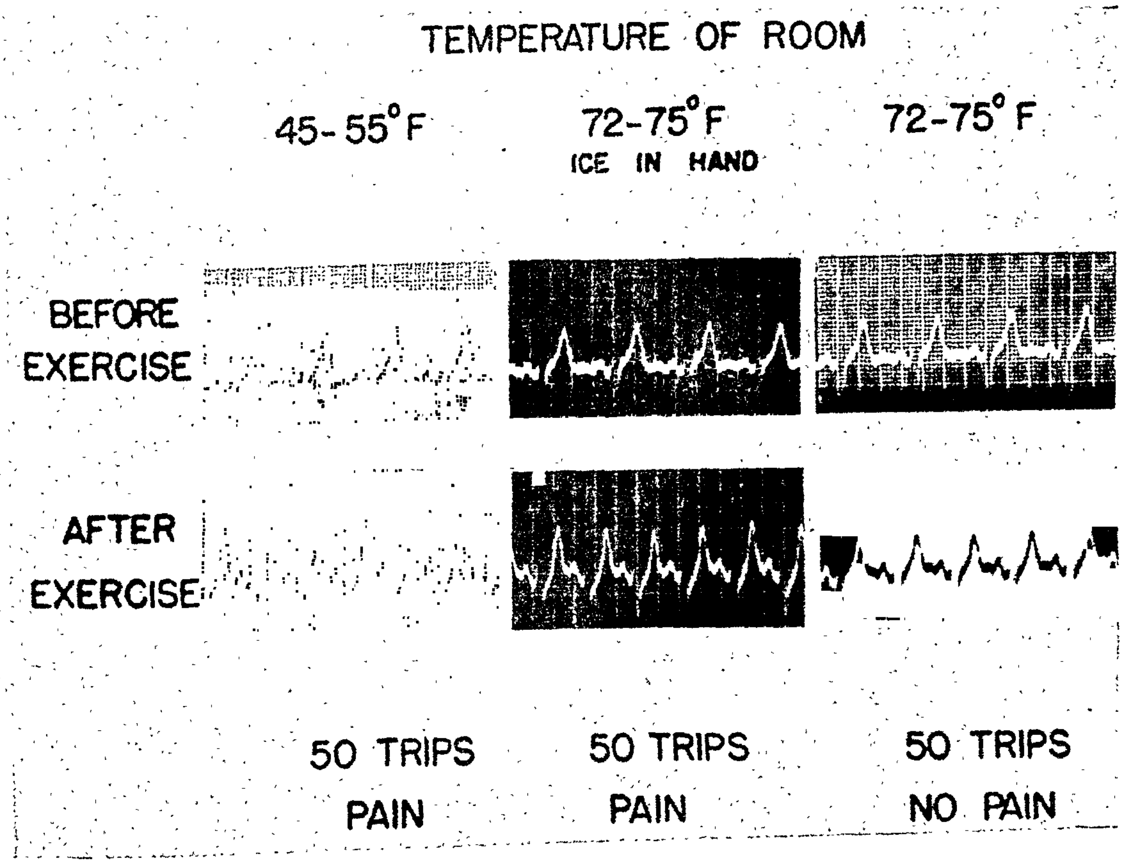

Fig. 2.

sponded to heat or nitroglycerin showed, in the cold room, an increased depression of 1.2 to 1.7 mm. in the S-T segment in Lead IVR, as compared to the findings when the same amount of exercise was carried out at ordinary room temperatures (Table V, Fig. 2). Tracings obtained on eleven subjects who exercised at room temperature while grasping an ice cube were similar to those during exercise under the usual standardized conditions in the constant cold temperature room (Table VI, Fig. 2).

TABLE V

COMPARISON OF THE S-T SEGMENT CHANGES* AFTER THE SAME AMOUNT OF WORK PERFORMED IN THE COLD TEMPERATURE ROOM (45 TO 50° F.) AND AT ROOM TEMPERATURE (72 TO 75° F.)

PATIENT	ROOM TEMPERATURE 45 TO 50° F.		ROOM TEMPERATURE 72 TO 75° F.	
	NUMBER OF TRIPS	S-T SEGMENT CHANGES* (MM.)	NUMBER OF TRIPS	S-T SEGMENT CHANGES* (MM.)
H. Schr.	26	-1.5	26+†	0
S. R.	50	-2.7	51+	-1.0
L. W.	36	-2.7	36+	-1.5
S. W.	38	-1.7	38+	-1.7
M. L.	40	-1.8	40+	-2.0
H. Schl.	54	-2.5	54+	-2.5
P. R.	44	-3.5	44+	-3.0
B. A.	50	-4.0	50	-4.0
V. B.	32	+2.0	32+	+1.5

*Average of ten consecutive complexes.
†+ = Patient stopped on request.

TABLE VI

COMPARISON OF THE EXERCISE TOLERANCE AND S-T SEGMENT CHANGES DURING EXERCISE IN THE COLD ROOM (45 TO 50° F.) AND AT ROOM TEMPERATURE (72 TO 75° F.) WHILE GRASPING AN ICE CUBE

PATIENT	ROOM TEMPERATURE 45 TO 50° F.		ROOM TEMPERATURE 72 TO 75° F. ICE CUBE IN HAND	
	NUMBER OF TRIPS	S-T SEGMENT CHANGES* (MM.)	NUMBER OF TRIPS	S-T SEGMENT CHANGES* (MM.)
R. C.	26	-1.0	18	-0.8
R. S.	22	-1.2	23	-1.2
W. Schr.	26	-1.5	32	-2.0
S. W.	28	-1.7	29	-1.5
M. L.	40	-1.8	37	-1.3
L. W.	40	-2.7	39	-3.3
S. R.	50	-2.7	47	-3.3
H. B.	78	-3.0	83	-2.5
P. R.	44	-3.5	35	-4.0
B. A.	50	-4.0	50	-4.0
V. B.	32	+2.0	32	+2.0

*Average of ten consecutive complexes.

Holding an ice cube for six or seven minutes while seated at rest caused no appreciable changes in the electrocardiograms of four patients; angina was not induced by this procedure. In 3 cases in which there was an increased exercise tolerance after heat or nitroglycerin, drinking 200 to 400 c.c. of ice water caused no precordial pain[5] or change in the S-T segment in the electrocardiogram. One of these 3 patients with angina and 3 of 8 normal subjects[6] developed a decrease in the amplitude, or inversion, of the T wave in Lead III.

In 2 cases, in which, at ordinary room temperature, the patients performed 40 per cent of the work previously shown to cause angina pectoris in the cold, the subsequent application of ice to the skin of the hands or abdomen caused no changes in the electrocardiogram which were different from those which occurred after similar work without the application of ice.

DISCUSSION

The results of the present study corroborate earlier clinical[7-9] and laboratory[1] observations on the striking effects of cold on patients with angina pectoris. Patients who do not experience angina during exercise at room temperature develop a typical attack at the same room temperature during exercise while holding an ice cube. This observation parallels the experience of many patients who, although warmly clothed and with only the face exposed, nevertheless have many more attacks of pain in winter than in summmer. A definite decrease in exercise tolerance may be observed in as short a time as ten seconds after the ice is grasped. Consideration of the mechanisms which might be responsible for the observed phenomena leads to the conclusion that a reflex factor is involved. Obstruction of the circulation in the hand holding the ice cube does not obliterate the effect of cold, which eliminates chilling of the blood as a cause for the exacerbation of angina by cold. The decrease in exercise tolerance that is observed when an ice cube is held in one hand cannot be psychic in origin, for it was possible to repeat the experiment many times with identical results. Pain and discomfort are not factors in this decrease in exercise tolerance, for holding an ice cube is not necessarily painful; heat, although it is often equally uncomfortable, has an effect opposite to that of cold, and the previous local application of heat abolishes the effect of local or generalized cold. Studies of the changes in heart rate and blood pressure at rest and during exercise with exposure to generalized and locally applied cold have not yielded data which permit one to ascribe the results to these factors. Accordingly, an increase in cardiac work caused by increased peripheral resistance cannot be considered an adequate cause of the observed reduction in exercise tolerance which follows the local application of ice. Similarly, increased cardiac work caused by increased output can be ruled out by the studies of Grollman.[10] It appears, therefore, that the factor responsible for exacerbation of angina by cold is reflex in origin, and may involve constriction of the coronary arteries or failure of vasodilatation. It is of interest in this regard that cooling of the skin of cats causes reflex vasoconstriction in the intestine.[11]

The present study presents objective data in support of the concept that coronary artery vasomotor changes, probably reflex in origin, exert a contributory influence in the precipitation of attacks of angina pectoris. Spasm of the coronary arteries could explain the precipitation of attacks by emotion, the occurrence of anginal pain after meals[7-9, 12] or with cholecystitis,[13] and the increased frequency of attacks during the winter months. The studies of Schlesinger[14] and Blumgart, Schlesinger, and Davis[15] show that the coronary collateral network usually includes segments of vessels with relatively little arteriosclerosis. Therefore, the possibility of vasoconstriction and vasodilatation in these nonrigid anastomotic vessels cannot be disregarded.

It has been demonstrated that the nitrites, including nitroglycerin, are coronary artery vasodilators.[16-22] The use of these substances enables many patients with angina pectoris to do considerably more work; electrocardiograms in such instances show less change in the S-T segment during exercise with medication than without it.[3, 23] Similarly, the local or general application of heat enables many patients with angina pectoris to do more work in the cold; this increase in exercise tolerance may likewise be accompanied by less change in the S-T segment during exercise. It is to be noted that every patient who showed an increase in exercise tolerance after receiving nitroglycerin responded similarly to the prior application of heat. The degree of response to heat and nitroglycerin is similar in the vast majority of patients. It has been shown[24] that immersion of the arm in a warm bath does not significantly change the cardiac output. These observations suggest that heat acts as a coronary vasodilator; this may occur reflexly.

A group of patients were found to exhibit no change in exercise tolerance after the general or local application of heat (Table I); they likewise did not respond to the vasodilator drugs (Table I). In general, this group is characterized by a low exercise tolerance. The expectation of life of these patients appears to be less, in our experience, than that of patients who respond favorably to the administration of vasodilator drugs.[25] Since the syndrome of advanced angina pectoris is always associated with extensive disease of the coronary arteries,[14, 15] it is not unexpected that certain persons fail to show effects which we consider to be vasomotor in origin.

The prophylactic use of locally applied heat (hot water or Thermat pad) obliterates the effect of local or generalized exposure to cold and enables some patients to do much more work in the cold. This phenomenon may be of value in the prevention of attacks in daily life. For instance, one patient, F. G., a chauffeur, aged 50 years, frequently experienced angina while driving in cold weather. He was able to drive without experiencing pain if he placed a chemical heating pad against his abdomen before he left his home. Clinicians in the past have made similar observations. For example, Parry stated that patients with angina pectoris were to avoid "want of circulation in the extremities and skin, evinced by coldness of these parts. . . It ought therefore to be guarded against by proper clothing. . . , so as to keep the whole body dry and warm."[26] Other authors[24, 27] have recommended the use of heat over the sternum, or baths, to relieve the pain of angina pectoris.

The fact that most patients, when exercising under standardized conditions in the cold, develop typical attacks, and that the amount of exercise necessary to induce such an attack in a given instance is remarkably constant has been utilized for the study of angina pectoris in this laboratory. A disadvantage of the standardized exercise tolerance test as described is the need for a constant-temperature cold room. The present study shows that this can be obviated by having the patient

hold an ice cube in one hand during exercise at ordinary room temperature; the results are similar to those which are observed under the standardized conditions in a constant-temperature cold room.

This study again emphasizes the importance of utilizing cold in the precipitation of attacks of *angina pectoris in the laboratory.*[1]

SUMMARY AND CONCLUSIONS

1. Objective quantitative studies of the effects of heat and cold on patients with angina pectoris have been presented.

2. The local application of ice to the hand during exercise reduces the exercise tolerance of patients with angina pectoris, and results in the precipitation of pain in a warm room. This observation parallels the experience of many patients with angina pectoris who, although warmly clothed, and with only the face exposed, nevertheless have many more attacks of pain in winter than in summer.

3. The striking effect of the local application of cold may be demonstrated in ten seconds, is maximum in thirty to forty seconds after application, and cannot be prevented by obliteration of the venous return. Its effects are nullified by the prior application of heat or administration of nitroglycerin.

4. These studies lend support to the concept that coronary artery vasomotor changes, probably reflex in origin, exert a contributory influence in the precipitation of attacks of angina pectoris; and that heat acts as a coronary vasodilator and cold as a vasoconstrictor or to prevent vasodilatation.

5. The prophylactic use of heat enables many patients with angina pectoris to do considerably more work in a cold atmosphere, and suggests that the local application of heat may be of value in the prevention of attacks in daily life under certain circumstances.

6. The local application of ice may be utilized clinically as a substitute for a cold room in precipitating attacks of angina pectoris for diagnostic and other purposes.

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OCCUPATIONAL POTENTIALITIES OF CARDIAC PATIENTS

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THE incidence of hypertensive and arteriosclerotic heart disease is steadily growing as a consequence of the increase in the average age of the population.[1] Thus, there is a larger number of cardiac patients in the older age groups who must be cared for by their families or by governmental or philanthropic agencies, unless they can support themselves. In addition, rheumatic heart disease, although its general incidence is decreasing, still continues to cause disability, as well as death, among young persons,[2,3] and therefore presents a problem of vocational guidance and training.

Cardiovascular diseases, in general, progress slowly; consequently, many cardiacs can look forward to a considerable number of years of survival after their disease is discovered. Patients with hypertensive heart disease will, in the majority of cases, show evidence of the disease in the fifth decade, and thereafter may count on ten or more years of comparatively normal existence. The average age of onset of arteriosclerotic heart disease is in the sixth decade, and several years of economic productivity are usually possible before the necessity for retirement occurs. Rheumatic heart disease will most often manifest itself in the second decade. Subsequently, the victim may live ten to fifteen years before severe congestive failure and incapacitation develop.[4]

The solution of the occupational problem depends upon several factors: first, an evaluation of the patient's functional and therapeutic status; second, the type of occupation for which he has been trained; third, the necessity for self-support; and, fourth, his emotional reaction toward his disease. These factors make the question of economic rehabilitation an individual problem for each patient, and make it difficult to offer any set rule for the type and amount of work a patient with heart disease can do.

In 1941, in conjunction with the New York Heart Association and the Bellevue Hospital Adult Cardiac Clinic, we initiated a program which, it was hoped, would eventually produce answers to the following questions: (1) What types of occupation are best suited to persons with heart disease? (2) What effect do various occupations have on the course of heart disease?

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Received for publication May 1, 1943.

EMPLOYMENT STATUS OF PERSONS WHO WERE ATTENDING ADULT CARDIAC CLINICS IN NEW YORK CITY

In order to establish a background for the study, the charts of 2,081 patients who were attending ten New York Heart Association adult cardiac clinics were reviewed with reference to type of heart disease, functional and therapeutic classification, and occupation.* Since these patients had a comparatively small income, any conclusions drawn from this study will be applicable only to similar economic groups.

Table I shows that, of the 2,081 patients who were attending the adult cardiac clinics, approximately half were males and half females. In age distribution, 26 per cent were under 35 years of age, 36 per cent were between 35 and 54, and 38 per cent were 55 and over. The average age of the women was less than that of the men.

TABLE I

AGE AND SEX DISTRIBUTION OF 2,081 PATIENTS WHO ATTENDED THE NEW YORK HEART ASSOCIATION ADULT CARDIAC CLINICS IN 1941

AGE	MALE		FEMALE		TOTAL	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
0 —34	226	22	317	30	543	26
35—54	325	32	417	39	742	36
55 and over	468	46	328	31	796	38
All ages	1019	100	1062	100	2081	100

Table II shows that 84 per cent of the women and 47 per cent of the men were working in 1941. The proportion of women who were working was high because women who did their own housework were classified as working, and also because the average age of the women was less than that of the men. The percentage of men who were working decreased greatly with age, whereas the percentage of women who were working decreased only slightly in the oldest age group. This difference is undoubtedly due to the fact that older men cannot obtain employment easily, whereas women can always do housework.

TABLE II

PROPORTION OF PATIENTS WHO WERE WORKING IN 1941

AGE	PER CENT WORKING		
	MALE	FEMALE*	TOTAL
0 —34	81	87	84
35—54	51	89	72
55 and over	25	75	46
All ages	47	84	65

*Includes housewives.

Ninety housewives who were attending the Bellevue Hospital Adult Cardiac Clinic were interviewed in order to ascertain the amount of work involved in keeping house. Table III shows that only 28 per cent of the women did no housework or did very light work. Seventy-two

*The authors are indebted to Miss Claire Lingg, of the Research Committee of the New York Heart Association, under whose auspices the charts were reviewed.

per cent performed what was considered the equivalent of a day's work in industry. The number of rooms and people in the household and the assistance provided by other members of the family were taken into consideration in estimating whether the amount of housework was light, moderate, or heavy.

TABLE III

AMOUNT OF WORK PERFORMED BY 90 HOUSEWIVES WHO WERE QUESTIONED AT THE BELLEVUE HOSPITAL ADULT CARDIAC CLINIC

	PERCENTAGE DISTRIBUTION
No work at home	8
Light cooking or cleaning	20
Moderate cleaning and cooking	34
Heavy cleaning and cooking	38

Table IV shows the occupational classification* of patients who were working in 1941. Forty-two per cent of the men were engaged in skilled or semiskilled work, and 29 per cent in unskilled work. A considerably larger proportion of men than women did professional, clerical, skilled, or semiskilled work. This proportion remained nearly constant with advancing age in the male group, but dropped almost to zero after the age of 34 years in the female group. As the age increased, the proportion of men in unskilled work increased. Before the age of 35 years, a comparatively large percentage of both the men and women were still students. Seventy-eight per cent of all the women and 90 per cent of those over 35 years of age did only their own housework.

TABLE IV

OCCUPATIONAL CLASSIFICATION BY AGE AND SEX OF 1,358 PATIENTS WHO WERE WORKING IN 1941

OCCUPATION	PERCENTAGE DISTRIBUTION							
	MALE				FEMALE			
	0—34	35—54	55 AND OVER	ALL AGES	0—34	35—54	55 AND OVER	ALL AGES
Professional, clerical	18	23	18	21	15	2	2	6
Skilled, semiskilled	32	46	44	42	12	5	2	6
Unskilled	15	31	38	29	1	3	3	3
Housewives	—	—	—	—	51	90	93	78
Students	35	0	0	8	21	0	0	7

Table V shows the proportion in each etiological group by age. Fifty-one per cent of the patients had arteriosclerotic or hypertensive heart disease, 39 per cent had rheumatic, and 10 per cent, syphilitic, heart disease. The majority of patients between the ages of 1 and 34 years were rheumatics. Between the ages of 35 and 54 there were approximately equal proportions with rheumatic and degenerative heart

*The occupations were classified according to the outline in "Death Rates by Occupations," edited by Jessamine S. Whitney (National Tuberculosis Association). Examples of occupations which fall into the different classifications are as follows:

Skilled—butcher, electrician, mechanic, painter, etc.

Semi-skilled—baker, chauffeur, operator in manufacturing industries, etc.

Unskilled—all types of laborers, domestic servants, and maintenance helpers.

disease, whereas the majority of the oldest patients suffered from some form of degenerative heart disease. From the point of view of occupational potentialities, it is important to keep in mind that 74 per cent of the patients who were attending adult cardiac clinics were over 35 years of age (see Table I) and 51 per cent had a degenerative form of heart disease. Thus, they constituted a group which had probably worked at a particular job for many years before the discovery of their heart disease. The learning of new techniques by such persons would be difficult.

TABLE V

KIND OF HEART DISEASE AND AGE AND SEX OF 2,081 PATIENTS WHO ATTENDED THE NEW YORK HEART ASSOCIATION ADULT CARDIAC CLINICS IN 1941

KIND OF HEART DISEASE	PERCENTAGE DISTRIBUTION 0—34	35—54	55 AND OVER	MALE	FEMALE	TOTAL
Rheumatic	97	43	4	27	51	39
Syphilitic	2	16	8	13	6	10
Degenerative*	1	41	88	60	43	51

*Includes hypertensive heart disease, arteriosclerotic heart hisease, and combined hypertensive and arteriosclerotic heart disease.

Table V also shows that hypertensive and arteriosclerotic heart disease was more prevalent among men than among women (60 per cent and 43 per cent, respectively). Conversely, rheumatic heart disease was more frequent among women (51 per cent and 27 per cent, respectively). Syphilitic heart disease was more frequent among men than women.

Table VI shows the proportion of men and women in each etiological group who were working. Among the men, 70 per cent with rheumatic, 51 per cent with syphilitic, and 26 per cent with degenerative, heart disease were working. This variation is undoubtedly related to the age differences among the various etiological groups (see Table V). Among the women, the proportion who were working was relatively high for every type of heart disease. This was because of the large number of women who were doing housework.

TABLE VI

ETIOLOGICAL DISTRIBUTION OF PATIENTS WHO WERE WORKING

KIND OF HEART DISEASE	PERCENTAGE WORKING MALE	FEMALE
Rheumatic	70	90
Syphilitic	51	80
Degenerative	26	75

Table VII presents the occupational classifications, subdivided according to the cause of the heart disease. Among the men, about the same proportion with each type of heart disease were employed in professional or clerical work. A lower proportion of rheumatics than of any other type were employed in unskilled work, and a considerable pro-

portion of rheumatics were students. These differences are related to age because a higher percentage of older than of younger persons performed unskilled work. A large percentage of the women with every type of heart disease were doing their own housework. The proportion of housewives was greater in the syphilitic group than in the rheumatic group, and still greater in the degenerative group. These variations are also undoubtedly related to the age of the patients.

TABLE VII

OCCUPATIONAL CLASSIFICATION AND KIND OF HEART DISEASE OF 1,358 PATIENTS WHO WERE WORKING IN 1941

OCCUPATION	PERCENTAGE DISTRIBUTION					
	MALE			FEMALE		
	RHEUMATIC	SYPHILITIC	DEGENERATIVE	RHEUMATIC	SYPHILITIC	DEGENERATIVE
Professional, clerical	21	22	18	7	9	2
Skilled, semiskilled	36	41	48	7	4	3
Unskilled	20	37	34	3	7	2
Students	23	0	0	11	0	0
Housewives	–	–	–	72	80	93

The functional capacity of the heart was estimated from the patient's appraisal of his ability to perform physical activity. It is divided into the following classifications:

Class I —No limitation of physical activity.
Class II —Slight limitation of physical activity.
Class III—Marked limitation of physical activity.[5]

TABLE VIII

PERCENTAGE, BY AGE AND FUNCTIONAL CLASSIFICATION, OF PATIENTS WHO WERE WORKING

AGE	MALES FUNCTIONAL CLASSIFICATION			FEMALES FUNCTIONAL CLASSIFICATION		
	I	II	III	I	II	III
0-34	87	73	45	89	86	70
35-54	65	56	21	94	91	83
55 and over	41	29	15	85	81	67
All ages	70	47	18	90	87	73

Table VIII shows, in percentages, the age and functional capacity of the patients who were working. Among the men, the percentage who were working decreased as the functional capacity decreased, but, even in Class III, in which there was marked limitation of physical activity, a considerable number were employed. In every functional class, as the age of the male patients increased, the number who were working decreased. Among the women, there was a comparatively slight decrease in the number who were working, either as the limitation of activity became more marked or as age increased. Since functional capacity denotes the patient's appraisal of his physical limitations due to his cardiac disability, it is apparent that the functional capacity was not

always the deciding factor as to whether or not the patients worked. Among the men, economic necessity, and, among the women, the size of the family and the necessity for running the house are usually the deciding factors as to whether or not the patient works.

Table IX shows the occupational distribution of the four functional classes. On the whole, as the functional capacity of the patients declined, the proportion engaged in unskilled labor increased, and the proportion of students and those who did professional and clerical work decreased. The number employed in skilled and semiskilled work was highest in Class II. It may be assumed that skilled and semiskilled jobs require more physical labor than do professional, clerical, or student's work, and that unskilled jobs require more physical work than skilled or semiskilled ones. Thus, in this group, a large proportion of patients with the least amount of cardiac reserve apparently did not possess the vocational training to permit them to do anything except unskilled labor in order to earn their livelihood. Cardiacs in Class III were, in the main, older than those in I and II, and it appears that, in this clinic group, older persons had not had as much opportunity as young ones to learn clerical or skilled trades.

TABLE IX

OCCUPATION AND FUNCTIONAL CLASSIFICATION OF PATIENTS WHO WERE WORKING IN 1941

OCCUPATION	PERCENTAGE DISTRIBUTION					
	MALES			FEMALES		
	FUNCTIONAL CLASSIFICATION			FUNCTIONAL CLASSIFICATION		
	I	II	III	I	II	III
Professional, clerical	18	17	9	10	5	2
Skilled, semiskilled	37	47	40	12	6	1
Unskilled	22	28	51	3	3	1
Students	23	8	0	18	3	0
Housewives	—	—	—	57	83	96

This analysis brings out some of the problems which are met when attempts are made to evaluate the occupational potentialities of cardiacs. The major problem of the cardiac patient in industry is to obtain a job which does not tax his cardiac reserve and will not adversely affect the progress of his heart disease. When rheumatic heart disease is discovered during the early life of a child, it is possible to train him in an occupation which will not be too great a tax on his physical limitations, but when hypertensive or arteriosclerotic heart disease is discovered after the age of 40 years, it is difficult for the patient to learn a new trade which requires less physical labor.

Before jobs can be found for persons with heart disease, occupations must be evaluated according to the amount of physical labor involved. A classification of clerical, skilled, semiskilled, and unskilled labor is not sufficient. The evaluation of such factors as the number of working hours per week, the amount of lifting, climbing, and carrying

involved, and the traveling time per day is necessary in order to ascertain how strenuous an occupation is. The work limitation of cardiacs must be analyzed in terms of actual occupations. This can be done only by obtaining exact information about the physical labor performed in a job, placing a cardiac of known functional and therapeutic classification in that job, and carefully following the progress of the patient's heart disease. With these facts in mind it was considered advisable to establish a service which would ascertain the effect of specific jobs on the physical capacity of cardiac patients.

EMPLOYMENT OF CARDIAC PATIENTS

In April, 1941, in conjunction with the Handicapped Division of the United States Employment Service and the New York Heart Association, a "Work Classification Unit" was organized as part of the Adult Cardiac Clinic of Bellevue Hospital.* The following types of patients were referred to the Work Classification Unit by the Handicapped Division:

1. Persons registered for placement with the United States Employment Service who gave a history of cardiac disability and did not have, and were unable to obtain, an adequate cardiac examination.

2. Persons with heart disease who were applying for employment and had had a contradictory or inadequate cardiac diagnosis.

3. Persons who were employed in jobs which, in the opinion of the Handicapped Division, were not consistent with their cardiac classification; for example, a Class III patient employed as a day laborer.

4. In recent months, persons rejected by the Selective Service Board for heart disease, who were seeking employment.

Th patients referred to the Work Classification Unit received the routine work-up for new patients. This consists of a complete social and medical history, physical examination, electrocardiogram, roentgenographic and fluoroscopic examination, serologic test for syphilis, and urine analysis. Additional laboratory procedures were done when necessary. A report of the cardiac diagnosis and an opinion as to the advisability of continuing the present occupation or suggestions as to suitable employment were sent to the Handicapped Division.

Several weeks after the patient received employment, he was visited at his place of occupation, and information was obtained concerning the type of occupation, the patient's opinion of the work, the salary, the number of working hours per week, the traveling time per day, the amount of lifting, carrying, and climbing, and the environmental sanitation of the plant.† An attempt is made by the Work Classification Unit to examine the patients at intervals of six months, and to evaluate the progression of their heart disease in relation to their occupation.

*The authors are indebted to Dr. Clarence de la Chapelle, Professor of Clinical Medicine, College of Medicine, New York University, who permitted the establishment of the Work Classification Unit at the Thursday Night Adult Cardiac Clinic of the Third Division of Bellevue Hospital.

†For the purposes of this study, environmental sanitation includes heat, light, ventilation, dust, fumes, dampness, noise, and cleanliness.

In the period from April, 1941, to October, 1942, the Work Classification Unit diagnosed and suggested jobs for 110 patients. Table X gives the age and etiological classification of these patients.

TABLE X

AGE AND KIND OF HEART DISEASE OF 110 PATIENTS WHO ATTENDED THE WORK CLASSIFICATION UNIT FROM APRIL, 1941, TO OCTOBER, 1942

KIND OF HEART DISEASE	0-34 (YEARS)	35-54 (YEARS)	55 AND OVER (YEARS)	ALL AGES NUMBER	ALL AGES PER CENT
Rheumatic	43	7	0	50	45
Degenerative	1	11	10	22	21
Other*	5	1	1	7	6
No heart disease	18	9	4	31	28
Total	67	28	15	110	100

*Includes congenital heart disease and heart disease of unknown cause.

More than half of these patients were under 35 years of age, and 45 per cent suffered from rheumatic heart disease. A relatively large percentage (28) were found to have no heart disease. These age and etiological distributions differ from those found in the 2,081 patients discussed above. The cardiac patients who are attending the Work Classification Unit are, in general, young people who are suffering from rheumatic heart disease and seeking advice about employment rather than medical aid. Thirty-nine per cent of the patients who were thought to have heart disease were in Class I (no limitation of physical activity), and 61 per cent were in Class II or Class III.

Table XI gives the functional classification and employment status for the previous twelve months of the patients who were referred for diagnosis. In Classes I and II the majority of patients *had worked* within the year, but in Class III only about one-fifth had worked.

TABLE XI

PERCENTAGE WHO WERE WORKING AND FUNCTIONAL CLASSIFICATION OF PATIENTS WHO ATTENDED THE WORK CLASSIFICATION UNIT*

FUNCTIONAL CLASSIFICATION	PERCENTAGE WHO WERE WORKING
Class I	85
Class II	80
Class III	18

*Exclusive of the patients diagnosed as having no heart disease.

The therapeutic classification serves as a guide in the management of patients. It is a prescription for the amount of physical activity which is advised by the physician. The therapeutic classification is divided as follows:

Class A—physical activity need not be restricted.

Class B—no unusually severe or competitive efforts.

Class C—ordinary physical activity moderately restricted.

Class D—ordinary physical activity markedly restricted.[2]

Table XII shows the customary occupations of the patients with respect to their therapeutic classification. The majority did work which required a comparatively great amount of physical effort. For example, 43 per cent of the patients who were advised not to engage in unusually severe or competitive efforts (Class B) were employed as manual laborers or waiters and waitresses. Fifty per cent of the patients whose ordinary physical activity should have been moderately restricted (Class C) were doing manual labor. An estimate of how much work a patient should do (the therapeutic classification) is of little value unless the patient can be provided with a job that does not require more work than is considered advisable.

TABLE XII

CUSTOMARY OCCUPATION AND THERAPEUTIC CLASSIFICATION OF 79 PATIENTS WHO ATTENDED THE WORK CLASSIFICATION UNIT

OCCUPATION	THERAPEUTIC CLASSIFICATION A*	B	C	D	TOTAL
Student	3	1	2	0	6
Salesman, clerk	0	8	5	1	14
Machine operator, mechanic	5	7	0	1	13
Packer, baker, dispatcher	2	1	3	0	6
Painter, carpenter, electrician	1	1	2	0	4
Taxi-driver	1	0	0	0	1
Errand boy, usher, messenger	1	2	1	0	4
Waiter, waitress	2	3	4	0	9
Unskilled laborer	4	12	6	0	22
Total	19	35	23	2	79

*Includes possible and potential heart disease.

Industrial follow-up records were made of twenty of the patients in the Work Classification Unit. Eighteen had rheumatic heart disease and two had hypertensive and arteriosclerotic heart disease. This distribution is undoubtedly due to the fact that seventeen of these patients were under 35 years of age. The majority were classed as IIB or IIC. In the majority of cases the type of occupation of the patient remained unchanged after his heart disease was classified. However, most of the jobs were of a sedentary nature, and, in the main, it was not considered necessary to change them. Seven typists and clerks, five machine operators, and two poster designers were advised to continue in the same jobs. One house painter was trained to become a machine operator. Five men had been doing manual labor. One was trained to be a typist, two were transferred to semiskilled jobs (packers), and two continued to do manual labor.

The average number of working hours per week was thirty-seven. Only three patients worked more than forty hours a week, and two of these were classified as having no limitation of physical activity. However, one patient, classified as IIB, was working, against advice, sixty hours per week at unskilled labor. The majority of the jobs entailed a moderate amount of lifting and carrying, but practically no walking or climbing.

The traveling time per day of most of the patients was excessive, averaging one and one-half hours. Only one patient did not remain in good health, and was forced later to quit his job because of his heart condition. All of the patients, with the exception of the one who was forced to quit work, considered that their occupation entailed only a light or medium amount of physical effort.

These patients have now been followed for periods ranging from three months to one year. All except one are working less than forty hours per week; this is their only restriction. They appear content with their work, and do not feel that they are taxing their functional capacity. From this limited survey it seems that cardiacs with a functional capacity of I or II and a therapeutic classification of A, B, or C can continue in a sedentary occupation without endangering themselves.

This project is only the first step towards a solution of the problem of cardiac patients in industry. The program must be expanded and carried on for several years before adequate criteria for the occupational limitations of persons with heart disease can be evolved. For this purpose, similar Work Classification Units should be established in other cardiac clinics.

Provisions must be made also to train persons with heart disease in occupations which will not tax their cardiac reserve. In the case of young people with rheumatic heart disease, vocational training can be offered by the public schools and convalescent homes. Special vocational schools for the older cardiac who has been working at an undesirable occupation should be established. In many cases, re-education of the employable person is impossible, and a compromise must be made by supplying him with a less strenuous job of the same type, or with one which has shorter working hours or requires less traveling time. It is important that cardiacs reside near their place of occupation, and thus conserve their energy for the job itself.

SUMMARY AND CONCLUSIONS

1. The charts of 2,081 patients who attended the New York Heart Association Adult Cardiac Clinics in 1941 were analyzed with respect to age, sex, type of heart disease, functional capacity, and occupation.

2. Eighty-four per cent of the females and 47 per cent of the males were working. The occupation of 78 per cent of the women consisted of housework. Forty-two per cent of the men were engaged in skilled or semiskilled work, and 29 per cent, in unskilled work. The proportion of men engaged in unskilled work increased with advancing age.

3. Fifty-one per cent of the patients had arteriosclerotic or hypertensive heart disease, 39 per cent had rheumatic, and 10 per cent had syphilitic, heart disease. Among the men, 70 per cent with rheumatic, 51 per cent with syphilitic, and 26 per cent with degenerative, heart disease were working. A higher proportion of men with degenerative and syphilitic heart disease than men with rheumatic heart disease were

employed in unskilled trades. A considerable proportion of the rheumatics were students. Among the women, the proportion who were working was high for every type of heart disease; the majority did housework.

4. As the functional capacity (the patient's appraisal of his ability to perform physical activity) decreased, the number of patients who worked decreased. Among those who were working, the worse the functional capacity, the higher was the proportion engaged in unskilled labor.

5. A Work Classification Unit was established at the Adult Cardiac Clinic of Bellevue Hospital for the purpose of classifying employable cardiacs who were referred by the Handicapped Division of the United States Employment Service and recommending jobs for them.

6. In the period from April, 1941, to October, 1942, 110 patients were diagnosed, classified, and recommended for jobs. Detailed analyses of the etiological, functional, and therapeutic classifications and occupations of these patients are presented.

7. Twenty patients from the Work Classification Unit were followed at their jobs. Observations were made as to the type of occupations, the number of working hours per week, the amount of traveling time per day, and the amount of lifting, carrying, climbing, and walking which was necessary in the various jobs. In this limited survey, it was found that patients with functional capacities of I or II and therapeutic classifications of A, B, or C can continue in occupations which require moderate physical activity and somewhat shorter than average working hours per week.

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THE PROBLEM OF RHEUMATIC FEVER IN THE NAVY

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RECENTLY a report[1] was made on the results of a "cardiovascular" survey of war casualties at the west coast United States Naval Hospitals at Oakland, Treasure Island, Mare Island, and San Diego, in December, 1942. This article is an amplification of that preliminary report. The cases of rheumatic fever studied at these hospitals were reviewed with regard to (1) the degree of disability produced by rheumatic fever in the Navy, (2) the frequency of rheumatic fever in the tropics, (3) the incidence of pre-existing rheumatic infections in childhood, and (4) recommendations concerning the acceptability for naval service of men who have had rheumatic fever.

In all, eighty cases of rheumatic fever were reviewed. About half of the patients were actually seen by the writer; the other half were studied by means of the hospital records and discussion with the chiefs of medicine and ward medical officers. The diagnoses were definite, and, in all the patients investigated, an acute, migrating polyarthritis was present, with fever, leucocytosis, increased sedimentation rate, and, usually, electrocardiographic changes. The average age was 21 years, and the range was from 17 to 25 years, except for three patients who were 30, 31, and 43 years of age, respectively.

The boys came from west coast training camps, from the South Pacific, from ships on which they had stood watch, from ships that were sunk near the Solomon Islands, etc. Some of the patients had suffered from prolonged immersion; others had experienced severe ordeals on Guadalcanal. The rain and dampness, with no adequate protection from the elements, the fatigue, both physical and mental, that resulted from the grind at a boot camp or in the actual combat areas; the herding together of large groups of men, usually with rapid turnover—all of this laid the the groundwork for a specific streptococcic infection of the upper respiratory tract. We thus have the classical background for attacks of rheumatic fever as portrayed by Coombs,[2] Swift,[3,4] Paul,[5] Coburn,[6] and Jones and Mote.[7] The attacks of rheumatic fever took place in both winter and spring, and so, all in all, they were of the textbook variety.

The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

Read at the joint session of the Section of Medicine, New York Academy of Medicine, and the New York Heart Association, New York, Jan. 21, 1943.

Received for publication May 5, 1943.

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To the Navy, rheumatic fever is a serious problem, and is being combatted energetically. The disease usually occurs sporadically, but outbreaks of epidemic proportions have taken place in the training stations at Newport and Great Lakes.[8] They have also been described in training centers in England.[9]

It is the general conception that rheumatic fever does not occur in the tropics, but the writer has always been of the opinion that it was there, and that either the disease was not diagnosed, or perhaps appeared in a different form from that which we are accustomed to seeing in this country. At the United States Naval Hospital at Oakland, California, there were nine cases of rheumatic fever which developed among our sailors and marines in the South Pacific. In the literature there is evidence that rheumatic infection is present in the tropics. Stott,[10] in a survey of post-mortem examinations in India, found that rheumatic heart disease was as frequent there as in London, and he concluded that the supposedly low incidence of rheumatic fever in India meant simply that the disease went unrecognized. Fernando[11] concluded that rheumatic infection was an important cause of heart disease in Ceylon, and accounted for one-fourth to one-fifth of the cardiovascular disease. The post-mortem incidence of rheumatic carditis appeared to be the same in the Colombo General Hospital as in Guy's and St. Mary's Hospitals, London. Chavez,[12] in a recent review of 2,400 cases of organic heart disease in Mexico, states: "The fact is emphasized that in Mexico, with its diversified, but predominently semitropical, climate, rheumatic heart disease is as prevalent as it is in England and the northern part of the United States. Attention is also called to the enormous incidence (61.9 per cent) of rheumatic heart disease in the poor and the Indian population (either pure or with a little admixture). This figure is probably not exceeded in any other country." The existence, therefore, of rheumatic heart disease presupposes the occurrence of rheumatic infection, and so the conclusion is justified that rheumatic fever occurs in the tropics.

The third point to be emphasized is the fact that 54 per cent of these patients who were seen on the west coast gave a history of one or more attacks of rheumatic fever in childhood. It would seem that the incidence may be higher if we consider the fact that so often there is no time for an adequate history when there is a large influx of casualties, and that often, under "past history," a statement is merely made that it is "negative" or "not relevant." In other words, the men with rheumatic fever have probably had this disease in childhood. The lowered resistance that comes with severe physical exertion and exposure, and is associated particularly with herding and rapid turnover of men, laid the groundwork for a severe upper respiratory infection by a hemolytic streptococcus, which was followed finally by rheumatic fever. This is simply a repetition of the view already held by many[3] that rheumatic fever is a continuous, chronic disease, with recrudescences.

Dr. T. Duckett Jones,[13] of Boston, in a study for the Navy of the cases of rheumatic fever which occurred in the Newport Training Station during the winter and spring of 1940–1941, found that 31 per cent, or nearly a third of the patients, gave a history of a previous attack of rheumatic fever in childhood.

Further evidence that the 54 per cent incidence of a history of a childhood attack of acute rheumatic fever in our eighty patients on the west coast is probably not too high is found in previous reports on rheumatic infection. A large majority of rheumatic fever attacks occur early in childhood, and this is indirect evidence that attacks of this disease which are observed in adult life are but a repetition of earlier disease or a lighting up of a chronic, dormant process. Thus, Coombs[2] found that "in about three-quarters of over 600 cases the onset took place during or prior to the fifteenth year of life, that is to say, during childhood; two-thirds of the whole number actually falling between the ages of 5 and 15." He pointed out that, among the older patients with established cardiac lesions, there was no history of any rheumatic infection, which shows that this may escape attention or be forgotten by the time adult life has been reached. Hedley[14] found that the first attack of rheumatic fever in at least 70 per cent of the cases occurred between the ages of 5 and 9 years. Cohn and Lingg have just made a statistical study of "The Natural History of Rheumatic Cardiac Disease," in which they state that "rheumatic fever may begin at any age, but it begins more often at about 8 years than at any other age. At 15, 70 per cent of persons afflicted have already acquired the disease." These investigators found that, of 1,050 patients whose valvular lesions were first noted some time after the age of 35 years, one-third gave a history of rheumatic infection in childhood or adolescence, but signs of cardiac disease did not appear until after the age of 35 years. Hence, two-thirds had no recollection of a rheumatic infection in previous years. Thus, the dormant, chronic nature of the lesion is illustrated, and indirect evidence is at hand that an attack of rheumatic fever in adult life presupposes a previous one in childhood.

To add significance to our 54 per cent incidence of a past history of one or more attacks of rheumatic fever in early childhood is the fact that, in a control series of 423 cases, there were only eight patients who had suffered from rheumatic fever in childhood, representing a 2 per cent incidence in the controls. These control cases were obtained in the same hospitals in which the rheumatic fever patients were or had been. They were of similar age groups, and consisted generally of the surgical patients with gunshot wounds, burns, amputations, appendectomies, herniotomies, etc. The histories of these controls were obtained by myself and other physicians who spoke individually to the marines and sailors; we explained our purpose and obtained complete cooperation from these men, who constituted an unusually intelligent group.

Finally, it should be remembered that patients often do not recall having had acute articular rheumatism; even the parents frequently do not.[4] Many an instance is seen of a patient with a negative past history, but with a large heart and significant murmurs, indicating previous heart disease.

From what has been said, it seems apparent that the majority of adults who are suffering from acute rheumatic fever have already had this disease in early childhood. The following case reports, which are typical of sailor and marine casualties of this war caused by rheumatic fever, were observed in the west coast hospitals, and illustrate the frequency with which a positive past history of this disease is obtained. Furthermore, it is evident that the crowding or herding at training stations and elsewhere, plus the arduous duties of general service in the Navy, with its lowering of resistance, and an upper respiratory streptococcus infection cause another attack of rheumatic fever.

CASE 1.— C. E. S., 18 years of age, enlisted Sept. 22, 1942, as a private in the United States Marine Corps. At the age of 14 years he had had scarlet fever, followed by acute polyarthritis. In September, 1941, he had had swollen, tender joints, and a diagnosis of "rheumatic fever" was made. In October, 1942, after sixteen days of training at the boot camp, he developed acute polyarthritis and was admitted to the San Diego Naval Hospital with a diagnosis of rheumatic fever.

CASE 2.—R. M. J., 19 years old, enlisted Dec. 27, 1940, as a seaman, second class. He was sent to the United States Naval Training Station at Great Lakes, Illinois, where he developed tonsillitis, followed by acute rheumatic fever. The following year, that is, in November, 1941, after standing watch at sea in the rain, his left ankle became swollen. The tenderness and swelling spread from joint to joint, and he was admitted to the United States Naval Hospital at Mare Island in January, 1942, with a diagnosis of acute rheumatic fever.

CASE 3.—J. E. L., 20 years of age, enlisted Jan. 20, 1942, as a seaman, second class. At the age of 6 years he had had "rheumatism," with joint pains, and was in bed thirty days. In 1935, he was in the County Hospital at Houston, Texas, for epistaxis and joint pains, and a diagnosis of rheumatic fever was made at that time. In October, 1942, while he was stationed at the United States Naval Air Station at San Diego, he developed a cold which was followed by epistaxis and joint pains. He was admitted to the San Diego Naval Hospital, Nov. 4, 1942, and acute rheumatic fever was diagnosed. Mitral stenosis and aortic insufficiency were found.

CASE 4.—C. W. L., 19 years of age, enlisted July 1, 1941, as an apprentice seaman, and, while stationed at the Alameda Air Station, developed pain in the joints of his feet. He was admitted to the United States Naval Hospital at Mare Island, Jan. 5, 1942, where he was found to have acute rheumatic fever, with a definite mitral lesion and roentgenologic evidence of enlargement of the heart. The history revealed that he had probably had attacks of acute rheumatic fever five and ten years before.

Case 5.—H. H., 23 years of age, enlisted Sept. 30, 1940, as a signalman, third class. (In 1936 he had had rheumatic fever.) He developed pain in one knee after five months spent on a strenuous Iceland patrol on the U.S.S. *Atlanta*. He had been through fog, cold, and rain. Although he suffered from pains in many joints, he did not report to the sick bay because he believed "they needed him." Although his ship passed through the Panama Canal to the west coast, he did not improve. He was admitted to the Oakland Naval Hospital in August, 1942, and was found to have acute rheumatic fever.

Case 6.—R. M. Z., 18 years of age, enlisted Dec. 27, 1940, as a seaman, second class. At the age of 15 years he consulted a physician for pains in the muscles and joints of both legs, and was told that he had a "leakage of the heart." At the United States Naval Training Station at Great Lakes, in February, 1941, he had acute tonsillitis and pains in his extremities. Finally, in November, 1941, after standing watch at sea for twelve hours in rainy weather, he developed a tender, red, swollen ankle, and the process spread from joint to joint. In January, 1942, he was admitted to the Mare Island Naval Hospital, where he was found to have acute rheumatic fever.

In many cases of seamen and marines who were suffering from acute rheumatic fever but gave no history of previous attacks, the physical signs made it probable that rheumatic valvular heart disease had been present before.

Case 7.—J. W. C. C., 21 years of age, enlisted Oct. 14, 1941. In April, 1942, he was admitted to the Mare Island Naval Hospital suffering from acute rheumatic fever, with painful, swollen ankles, knees, wrists, and elbows, accompanied by fever. However, his heart was found to be "distinctly enlarged" roentgenologically, and the electrocardiogram revealed a prolonged P-R interval, marked left axis deviation, high voltage of the QRS, and T-wave inversions. The left axis deviation and high voltage of the QRS were evidences that the cardiac enlargement must have been developing over a period of years.

Case 8.—R. E. C., at the age of 21 years, enlisted as a ship's cook, third class, Aug. 20, 1941. In the latter part of August, 1942, while on transport duty, during an engagement in the Solomon Island area, for three nights and days he worked hard and continuously in an atmosphere of excessive heat. He became short of breath and noticed that his ankles were swollen and tender. He reported at the sick bay, and was transferred to the U.S.S. *Solace*, and finally to the Oakland Naval Hospital. Here, a diagnosis of acute rheumatic fever was made; the electrocardiogram revealed lengthening of the P-R interval. However, in spite of a negative past history with respect to rheumatic fever, a diagnosis was made of long-standing rheumatic heart disease, with mitral valve involvement. Even when he was first transferred to the *Solace*, his heart had been found to be enlarged, and there was a loud, prolonged, harsh, systolic murmur at the mitral region. At that time, too, and subsequently, he had persistent hypertension, with readings of 158/100, 160/96, and 158/112.

Case 9.—E. A. B., 25 years of age, enlisted April 30, 1936, as a private in the Marine Corps. While stationed at Camp Elliott, California, he developed acute rheumatic fever and was transferred to the San Diego Naval Hospital. Although there was no previous history of rheumatic

fever, the patient had been told in 1936 that he had a "murmur" of the heart.

To add further confirmation to the conception that an attack of acute rheumatic fever in young adults may not be the first, it may be mentioned that ten patients were seen in the west coast Naval Hospitals with definite, chronic, cardiac valvular disease whose murmurs had been missed on enlistment. Five of these gave an authentic history of rheumatic fever in childhood, and the other five must have had a rheumatic infection which was unnoticed or forgotten. This is reasoning again that all adult patients with rheumatic fever have had the disease in early life.

It appears, then, that the congestion among recruits at training stations and elsewhere, particularly where there is a rapid turnover of men, the stress and strain, physical and mental, which are undergone in wartime in the training camps of our country, as well as in combat areas, cause a recrudescence or exacerbation of the latent rheumatic disease. This leads to the final point of this paper, that once a boy or man has had rheumatic fever he should not be accepted for general service in the Navy. Whether or not this can be applied to the selection of recruits remains to be seen. The number of applicants for enlistment who must be examined every day is so large that there is no time for taking detailed case histories in the recruiting stations. Furthermore, it is probable that the average young man who volunteers would not admit having had rheumatic fever if such a history were known to be disqualifying. Such histories might be obtained during the examination in the training stations after enlistment, but before the recruit entered general service. Captain Howard H. Montgomery, M.C., United States Navy, has suggested to me that it might be feasible, however, to consider an authentic past history of rheumatic fever as disqualifying a man for induction under Selective Service.

CONCLUSIONS

1. Rheumatic fever is a personal and epidemiologic problem in the Navy, and causes disability.

2. Evidence is produced that rheumatic fever occurs in the tropics.

3. A history of childhood infection was obtained in 54 per cent of eighty cases of acute rheumatic fever. Other data are cited to show that rheumatic fever in adult life probably represents a recrudescence of childhood disease.

4. Men who have had rheumatic fever, with or without residual heart murmurs, are subject to recurrence of active infection. It is recommended that candidates with a definite history of rheumatic fever be rejected for general military service.

I wish to thank Captain Howard Montgomery, M.C., U.S.N., and R. A. Luther Sheldon, Jr., M.C., U.S.N., for their criticisms and suggestions.

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THE EFFECT OF INTRAVENOUSLY ADMINISTERED DIGOXIN AND OUABAIN ON THE SYSTEMIC VENOUS PRESSURE OF PATIENTS WITH CONGESTIVE HEART FAILURE

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IT IS well known that congestive heart failure, particularly of the right-sided type, is accompanied by an elevated systemic venous pressure, and that this pressure returns to normal when circulatory compensation is regained. Both the recovery of circulatory compensation and the fall of the elevated venous pressure are believed to be rather slow processes. This appears to be true for the therapeutic measures usually employed today.

While studying the circulatory effects of purified cardiac glycosides, a very rapid fall of the elevated venous pressure was encountered when these drugs were administered intravenously to patients with congestive heart failure. The rapidity of this effect is in itself of interest, but more important are its implications, both from a therapeutic standpoint and from the theoretical viewpoint of the mode of action of digitalis and its purified components.

METHODS

The subjects of this study were hospitalized patients with organic heart disease of widely varying kinds and with various structural defects. All had congestive heart failure. The degree and the manifestations of this failure varied from subject to subject, but in all it was of sufficient severity to require complete bed rest. The patients received a "ward" diet, with salt limited to 3 to 5 Gm. per day. Neither fluid intake nor urine output was measured. In the absence of these measurements, the daily weight, ascertained at the same hour each day, was taken as a guide to fluid balance.

Venous pressure was measured in the antecubital veins by the direct method (Moritz and von Tabora), using a manometer filled with physiologic salt solution. Both the vein and the manometer were always leveled off at the same point, i.e., 5.5 cm. to 6 cm. posterior to the angle of Louis. The positions of the vein and manometer were repeatedly checked to insure against any change in their relationship to the trunk.

Systemic venous pressure is indicated by the pressure in the antecubital veins only when the latter pressure is not artificially elevated by such factors as physical discomfort, fear, dyspnea, coughing, and tenseness.[1] These symptoms are usually present during congestive heart failure, and disappear when circulatory compensation is regained. Thus, recovery from congestive heart failure can be accompanied by a lower-

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Supported in part by grants from Burroughs Wellcome and Company (U.S.A.) Inc., and Carroll Dunham Smith Pharmacal Company.

Received for publication May 28, 1943.

ing of the antecubital venous pressure merely as a result of the removal of those subjective factors which elevate venous pressure regardless of the state of the circulation. The considerable magnitude of the changes induced by these factors is often not appreciated, particularly in quick and hurried observations.

During the venous pressure measurements in this study, care was taken to make the patients comfortable, and distressing symptoms were eliminated as much as possible. To accomplish this, codeine or small doses of morphine were occasionally required.

The ventricular rate was counted, always for one full minute, by auscultation over the precordium. Arterial blood pressure was measured by the usual auscultatory method, employing a mercury manometer. Electrocardiograms were obtained by the standard limb leads. To ascertain the rate of the flow of urine, a catheter was placed in the urinary bladder and allowed to drain continuously. At ten-minute intervals the amount of urine collected was measured, removed, and recorded.

The above measurements were made frequently, and often simultaneously, throughout an adequate control period and for two to four hours after the injection of the glycoside. Thereafter, they were made daily or less frequently, as indicated by the progress of the patient.

In this study two of the most rapidly acting glycosides were used, namely, ouabain and digoxin.* They were always given intravenously in *single* doses. Whenever possible, the glycosides were given after the maximum degree of improvement had been attained by bed rest, sedatives, and oxygen therapy.

In some cases, the single dose of glycosides restored circulatory compensation. If compensation persisted after the patient became ambulatory, he was discharged on maintenance doses of whole-leaf digitalis. More often the therapeutic effect of a single dose was temporary or partial, and congestive heart failure of a more mild degree recurred. The same glycoside was then repeated in the same dosage. If its effects again proved temporary and the patient lapsed into a comparable state of circulatory failure, either of two courses was followed: (1) the same glycoside was repeated in a different dosage, or (2) a different glycoside was given in a dosage which was the gram-molecular equivalent of the first glycoside. The first of these procedures permitted a comparison of the effects of varying amounts of the same glycoside, and the second, a comparison of the effects of two glycosides, molecule for molecule.

RESULTS

Fourteen patients received, intravenously, twenty-one injections of digoxin, ranging from 0.5 mg. to 2.5 mg. per dose. Six of these patients had regular sinus rhythm, seven had auricular fibrillation, and one had auricular flutter. Three patients, all with auricular fibrillation, received, intravenously, five injections of ouabain in amounts ranging from 0.375 mg. to 0.75 mg. per dose. The larger doses of each glycoside produced toxic manifestations, chiefly in the form of irregularities of the heartbeat, and infrequently as gastrointestinal symptoms. The smaller and intermediate doses caused no toxic effects, yet often induced equally effective therapeutic results.

*The drugs used in this study were kindly supplied by Burroughs Wellcome and Company (U.S.A.), Inc. (digoxin), and Carroll Dunham Smith Pharmacal Company (ouabain).

PATIENTS WITH AURICULAR FIBRILLATION

Digoxin.—A very prompt fall of the elevated venous pressure followed eleven of the thirteen intravenously administered doses of digoxin (Table I). Of the two remaining cases, the venous pressure remained unaltered in one, but, in the other, fell to normal on the next day.

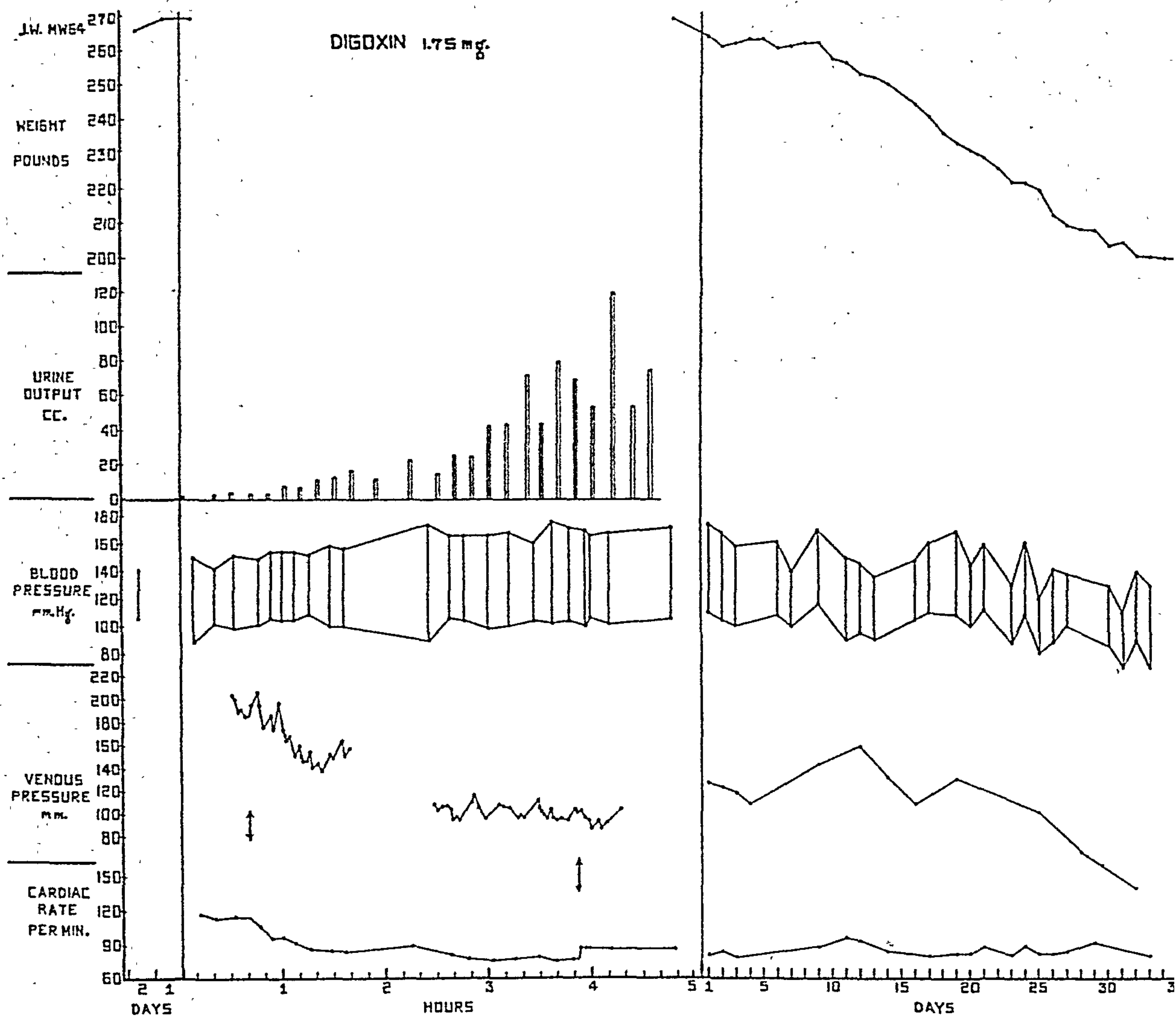

Fig. 1.—Effects produced by the intravenous injection of 1.75 mg. of digoxin. Severe congestive heart failure; arteriosclerotic heart disease, with auricular fibrillation. The response was of the very rapid and very favorable type.

All of the charts are similarly plotted: The two long vertical lines enclose the observations made on the day the drug was given. Observations on other days are beyond these lines. The heavy, vertical, double arrow on the left indicates administration of the glycoside; the double arrow on the right, atropine sulfate, 2 mg. intravenously.

The rapidity of the fall in venous pressure was striking. Five to twenty-two minutes after injection of the digoxin the venous pressure began to fall, continued to decrease progressively, and leveled off forty-seven minutes to three hours after injection. Seven times the venous pressure fell to a normal value. The other four times the fall was less marked, and the venous pressure leveled off at values which were definitely below the initial reading, but still higher than normal. On two of those four occasions the venous pressure fell to normal the next day; in the other two it remained at its lower, though still abnormal, value.

TABLE I

EFFECT OF INTRAVENOUSLY ADMINISTERED DIGOXIN ON THE VENOUS PRESSURE OF PATIENTS WITH CONGESTIVE HEART FAILURE AND AURICULAR FIBRILLATION

SUBJECT COLOR-SEX-AGE	DIAGNOSIS	DIGOXIN MG.	VENOUS PRESSURE: INITIAL LEVEL MM. SALINE	BEGINNING* EFFECT	MAXIMUM EFFECT	FINAL LEVEL MM. SALINE	% CHANGE	LEVEL NEXT DAY MM. SALINE	DURATION OF EFFECT
N. R. W—F—48	Rheumatic heart disease. Congestive heart failure (moderate)	0.5	139-153 (146) †	17 min.	2 hr., 22 min.	71-78 (75)	48.6	91-115 (108)	Congestive heart failure increased in 5 days with little change in venous pressure
N. R. W—F—48	Same	0.5	105-115 (110)	6 min.	50 min.	62-68 (65)	41.0	89	4 days
G. G. W—M—61	Hypertension and arteriosclerosis. Congestive heart failure (severe)	0.75	238-268 (258)	5 min.	2 hr., 25 min.	150-165 (157)	39.2	94-111 (103)	Patient discharged free of congestive heart failure
S. C. W—F—54	Arteriosclerotic heart disease. Congestive heart failure (moderate)	1.0	169-188 (177)	22 min.	48 min.	138-147 (140)	20.9	158-171 (163)	No appreciable response
S. C. W—F—54	Same	1.0	175-185 (180)	15 min.	47 min.	111-121 (116)	35.6	133-144 (138)	Less than 24 hours
J. G. W—M—38	Rheumatic heart disease. Congestive heart failure (severe)	1.0	225-242 (233)	13 min.	2 hr., 24 min.	140-145 (142)	39.0	77-94 (87)	10 days
P. D. W—M—49	Arteriosclerotic heart disease. Congestive heart failure (severe)	1.0	175-190 (182)			165-175		48.60	Mild congestive heart failure after 5 weeks

P. D. W—M—49	Same. Congestive heart failure (mild)	1.0	111-124 (117)	6 min.	57 min.	29-35	72.6	34-50 (45)	2 weeks
P. D. W—M—49	Same	1.0	95-120 (110)	8 min.	1 hr. 2½ min.	48-56 (52)	52.7		2 weeks
S. C. W—F—54	Arteriosclerotic heart disease. Congestive heart failure (moderate)	1.5	190-207 (201)	7 min.	50 min.	125-129 (127)	36.8	132-140 (136)	2 days
N. R. W—F—48	Rheumatic heart disease. Congestive heart failure (moderate)	1.5	208-218 (213)	14 min.	Between 2 hr., 30 min. and 3 hr., 42 min.	75-85 (80)	62.5	65-68 (65)	4 days
J. W. W—M—64	Arteriosclerosis and hypertension. Congestive heart failure (severe)	1.75	185-203 (194)	13 min.	2 hr.	93-97 (95)	51.0	123-132 (125)	Congestive heart failure did not return
M. H. W—M—58	Arteriosclerotic heart disease and hypertension. Congestive heart failure (severe)	2.5	196-205 (200)	Less than 15 min.	3 hr.	85-87 (86)	57.0	36-39 (38)	Compensation restored after single administration of drug. Still maintained one year later
				SUMMARY					
				5 to 22½ min.	47 min. to 3 hr., 42 min.		20.9 to 72.6		
				Case of Auricular Flutter					
J. B. W—M—65	Arteriosclerotic heart disease. Congestive heart failure (severe)	2.0	116-135 (125)	5 min.	72 min. (1 hr., 12 min.)	75-85 (80)	36.0		Patient expired several hours after drug was administered

*Beginning effect = the first venous pressure 10 mm. saline below lowest control value and followed by equally low or lower values.
†Most representative value is in parenthesis.

The most favorable responses were not only strikingly rapid, but persistent. In a typical instance (Fig. 1), the venous pressure fell from 195 mm. to 95 mm. of saline within two hours. Thereafter it remained at a normal level as the patient recovered compensation without further treatment. The fall in venous pressure was accompanied by an equally rapid slowing of the ventricular rate (from 117 to 84 per minute in one hour), and by a marked diuresis (6 c.c. to 8 c.c. per minute) which began two and one-third hours after the injection of the glycoside.

More often the responses, although of a similar pattern, were less rapid, less extensive, and less persistent in their quantitative effects (Fig. 2). The venous pressures fell promptly, but normal levels were not attained until the next day. Seemingly complete circulatory compensation then returned. In the course of the next five to fourteen days congestive heart failure reappeared, and the venous pressures again became elevated.

Ouabain.—Ouabain was administered intravenously five times. On each occasion there followed a very rapid and marked fall of the elevated venous pressure (Table II). This fall began three to eleven minutes after injection, and continued swiftly. Thirty-five to fifty-six minutes after injection the venous pressure had usually leveled off at a lower value. Twice this new level was normal. In the other three instances it was still higher than normal, but lower than the initial level. The rapidity of this response is indicated in a typical example (Fig. 3), in which the venous pressure fell from 250 mm. to 160 mm. of saline in forty-five minutes. A slowing of the ventricular rate (115 to 82 per minute) and an increase in the pulse pressure accompanied the change in venous pressure.

On all five occasions the beneficial effects were retained for only several days, after which the venous pressure rose and evidence of congestive heart failure reappeared.

When equal gram-molecular doses of digoxin and ouabain were given to the same patient during comparable states of congestive failure, ouabain induced its effects more rapidly than digoxin, but the final effects produced by the two drugs were of comparable magnitude (compare Figs. 2 and 3).

PATIENTS WITH REGULAR SINUS RHYTHM

Digoxin.—A prompt fall of the elevated venous pressure followed six of the seven intravenous injections of digoxin which were administered to six patients (Table III). In both rapidity and magnitude, the fall in venous pressure was comparable to that which occurred in cases of auricular fibrillation. The venous pressure began to fall four to nine minutes after injection, and leveled off at a lower value thirty-five minutes to two and one-half hours after injection. Twice the venous pressure fell to normal, and four times below the initial level,

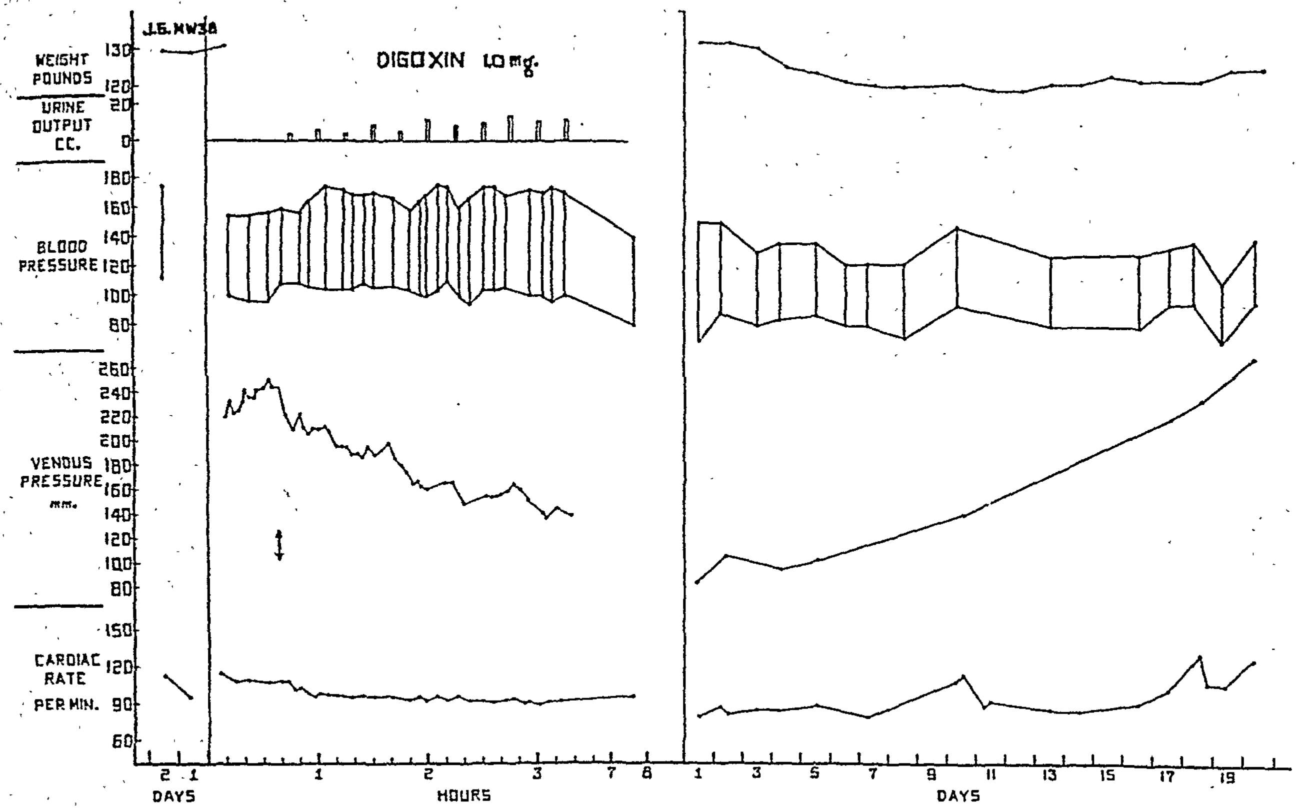

Fig. 2.—Effects produced by the intravenous injection of 1 mg. of digoxin. Severe congestive heart failure; rheumatic heart disease, with auricular fibrillation. The response was of the slower and more usually encountered type.

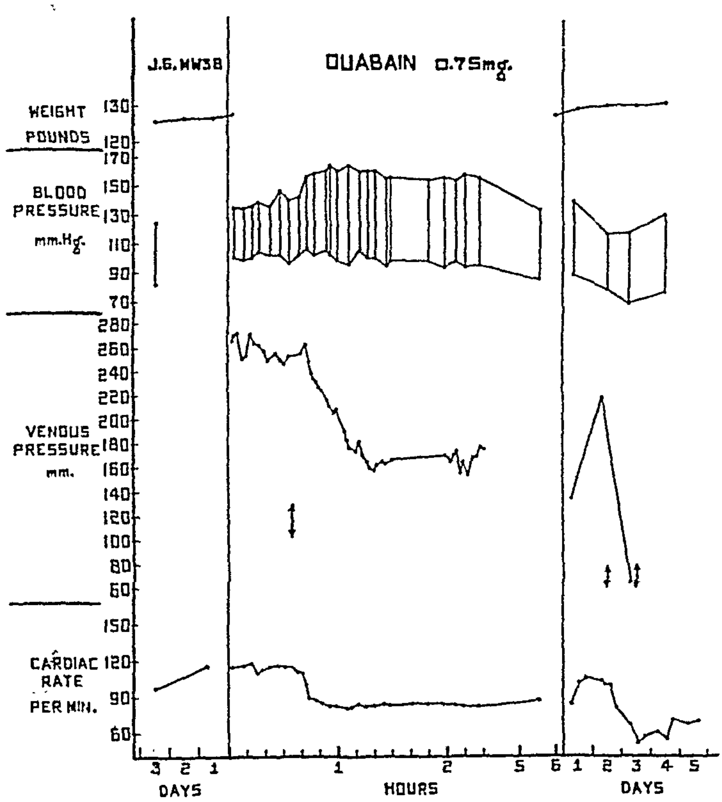

Fig. 3.—Effects produced by the intravenous injection of 0.75 mg. of ouabain. Moderate congestive heart failure; rheumatic heart disease, with auricular fibrillation. This patient had previously received 1 mg. of digoxin—see Fig. 2. The degree of congestive heart failure was now not quite as severe as when the digoxin was given. The two glycosides were administered in equal, gram-molecular amounts. Note that ouabain induced effects more rapidly. Between the two small vertical double arrows at the right the subject received 1.4 Gm. of whole-leaf digitalis by mouth.

TABLE II

EFFECT OF INTRAVENOUSLY ADMINISTERED OUABAIN ON VENOUS PRESSURE OF PATIENTS WITH CONGESTIVE HEART FAILURE AND AURICULAR FIBRILLATION

SUBJECT COLOR-SEX-AGE	DIAGNOSIS	OUABAIN MG.	VENOUS PRESSURE						DURATION OF EFFECT
			INITIAL LEVEL MM. SALINE	BEGINNING* EFFECT	MAXIMUM EFFECT	FINAL LEVEL MM. SALINE	% CHANGE	LEVEL NEXT DAY MM. SALINE	
N. R. W—F—48	Rheumatic heart disease. Congestive heart failure (severe)	0.375	138-150 (143)†	5½ min.	44½ min.	81-88 (84)	41.3	72-80 (72)	5 days
N. R. W—F—48	Same	0.375	151-161 (156)	2½ min.	36½ min.	83-88 (85)	45.5	76-82 (79)	4 to 5 days
J. G. W—M—38	*Rheumatic heart disease.* Congestive heart failure (severe)	0.55	267-278 (268)	5½ min.	35 min.	163-172 (168)	37.4	207-217 (212)	1 day
J. G. W—M—38	Same	0.75	248-252 (250)	11 min.	45½ min.	157-165 (162)	35.2	129-135 (132)	2 days
S. C. W—F—54	Arteriosclerotic heart disease. Congestive heart failure (severe)	0.75	230-235 (232)	3 min.	56 min.	123-128 (125)	46.1	193-204 (200)	1 day
			SUMMARY						
		0.375 to 0.75		3 to 11 min.	35 to 56 min.		35.2 to 46.1		

*Beginning effect = the first venous pressure 10 mm. saline below lowest control value and followed by equally low or lower values.
†Most representative value.

TABLE III

EFFECT OF INTRAVENOUSLY ADMINISTERED DIGOXIN ON THE VENOUS PRESSURE OF PATIENTS WITH CONGESTIVE HEART FAILURE AND NORMAL SINUS RHYTHM

SUBJECT COLOR-SEX-AGE	DIAGNOSIS	DIGOXIN MG.	VENOUS PRESSURE: INITIAL LEVEL MM. SALINE	VENOUS PRESSURE: BEGINNING* EFFECT	VENOUS PRESSURE: MAXIMUM EFFECT	VENOUS PRESSURE: FINAL LEVEL MM. SALINE	VENOUS PRESSURE: % CHANGE	VENOUS PRESSURE: LEVEL NEXT DAY MM. SALINE	DURATION OF EFFECT
W. L. W—M—59	Hypertension and arteriosclerosis. Congestive heart failure (severe)	0.5	82-89 (87)†						No effect obtained
H. S. W—M—51	Hypertension and arteriosclerosis. Congestive heart failure (severe)	1.0	217-238 (227)	8 min.	59 min.	120-129 (128)	43.5	151-166 (158)	2 days
J. J. N—M—32	Hypertensive heart disease. Congestive heart failure (severe)	1.0	126-142 (134)	Between 6 and 12 min.	2 hr.	57-60 (58)	56.7	109-119 (114)	1 day
F. P. N—F—52	Hypertensive heart disease. Congestive heart failure (severe)	1.5	187-197	4½ min.	2 hr., 27 min.	113-121 (118)	38.6	176-186 (180)	1 day
F. P. N—F—52	Same	2.0	185-200 (192)	5½ min.		148-155 (150)	21.8	140-155 (147)	2 days
J. W. N—M—54	Hypertension and arteriosclerosis. Congestive heart failure (severe)	2.0	108-118 (113)	5 min.	35 min.	55-65 (60)	46.9	47-49	3 weeks
J. G. W—M—56	Congestive heart failure (severe)	2.5	(230)	6½ min.	1 hr., 25 min.	164-170 (166)	27.8	212-238	1 day
			SUMMARY						
				4½ to 9 min.	35 to 147 min.		21.8 to 56.7		

*Beginning effect = the first venous pressure 10 mm. saline below lowest control value and followed by equally low or lower values.
†Most representative value.

but still above normal. In only one case did the normal venous pressure persist, and this patient recovered complete circulatory compensation. In the remaining five cases the venous pressure rose to its former high level after several days.

In a typical, marked response (Fig. 4), the venous pressure fell from 250 mm. to 120 mm. of saline within one hour. The ventricular rate did not change (114 to 120 per minute), but a marked diuresis (7 c.c. to 9 c.c. per minute) set in forty minutes after injection of the digoxin.

In cases of regular sinus rhythm, the response to intravenously administered digoxin differed from that in cases of auricular fibrillation in two respects: (1) the venous pressure fell without an accompanying change in ventricular rate, and (2) complete recovery of circulatory compensation was less frequent; the usual result was a temporary improvement in circulatory dynamics.

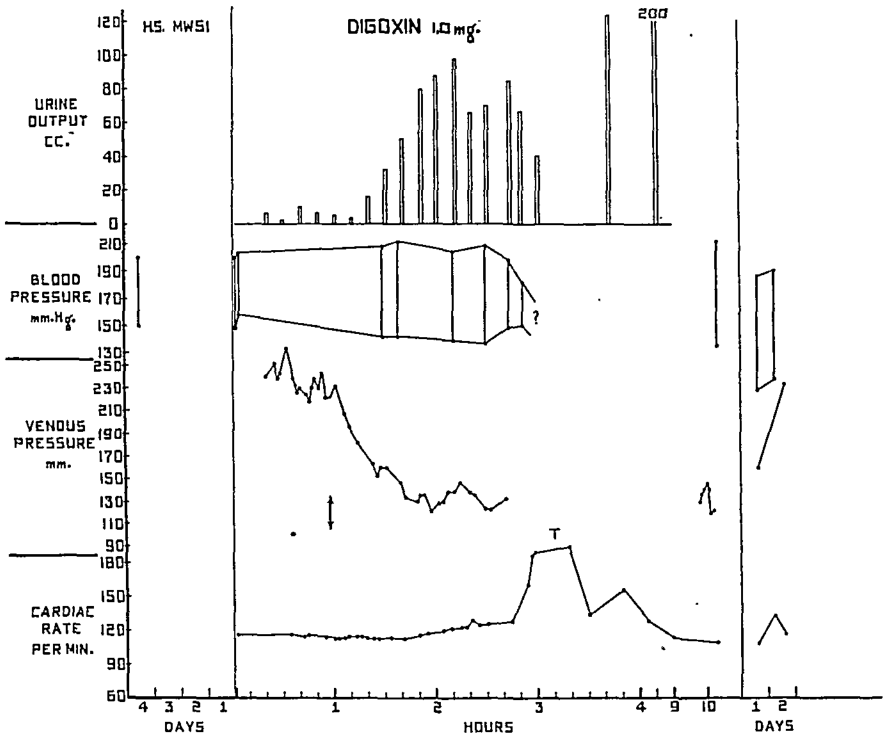

Fig. 4.—Effects produced by the intravenous injection of 1 mg. of digoxin. Severe congestive heart failure; hypertensive heart disease, with regular sinus rhythm.

The strikingly rapid diuresis and fall in venous pressure occurred without change in ventricular rate. During the period marked *T*, there was paroxysmal tachycardia of unknown type.

RELATIONSHIP OF THE FALL IN VENOUS PRESSURE TO OTHER OBSERVATIONS

Ventricular Rate.—In cases of auricular fibrillation, the fall in venous pressure usually began and progressed concurrently with a decrease in ventricular rate (Figs. 1, 2, and 3). This relationship was not an invariable one.

At times, the venous pressure continued to fall after the maximum reduction in ventricular rate had been attained (Fig. 3). On one oc-

casion (Fig. 5), a small dose of digoxin induced a prompt fall in venous pressure, during which the ventricular rate remained unchanged. Only after the venous pressure had leveled off at its lower value did the ventricular rate begin to slow.

When a glycoside had lowered the venous pressure and ventricular rate to normal levels, the intravenous injection of 2 mg. of atropine sulfate returned the ventricular rate completely or partially to its initial, rapid rate, but the venous pressure remained unaltered at its lowered value (Fig. 6).

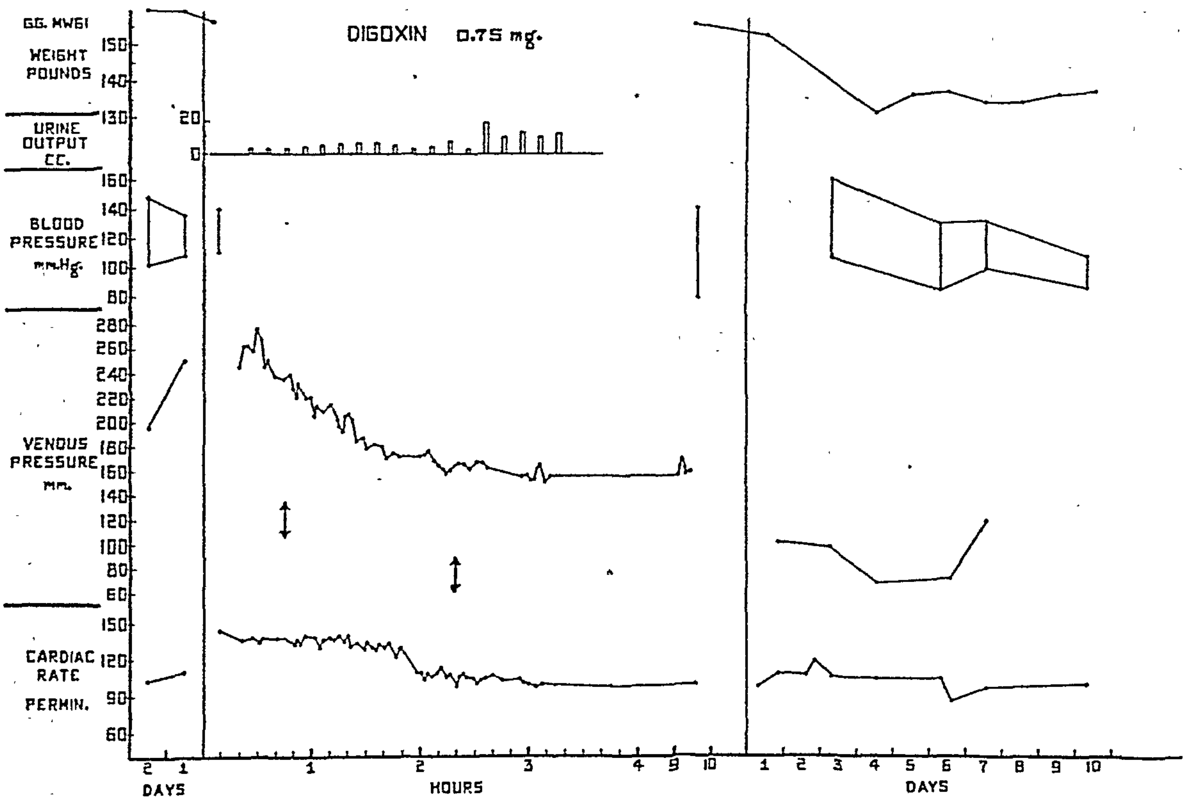

Fig. 5.—Effects produced by the intravenous injection of 0.75 mg. of digoxin. Severe congestive heart failure; arteriosclerotic heart disease, with auricular fibrillation.

At the first double arrow, patient received 0.5 mg. digoxin; at the second double arrow, 0.25 mg. The fall in venous pressure preceded cardiac slowing.

Irregularities of the heartbeat appeared not to alter the pattern of the fall in venous pressure. In a case of auricular fibrillation, 0.75 mg. of ouabain induced numerous premature ventricular contractions. These appeared six minutes after injection, quickly increased in number, and twenty minutes after injection were very numerous and were originating in varying foci (Fig. 7). Throughout this period the venous pressure fell precipitously and at a constant rate, whereas the ventricular rate, which had started to decrease sharply, fell less rapidly and less regularly (Fig. 7). Twenty-five minutes after injection, a regular, rapid rhythm (140 to 160 per minute) appeared. The electrocardiogram revealed ectopic tachycardia, with the focus in the bundle of His. In spite of this marked change in the mechanism of the heartbeat, the venous pressure continued to fall, but less precipitously. Shortly thereafter it leveled off (Fig. 7). After twenty minutes the tachycardia sud-

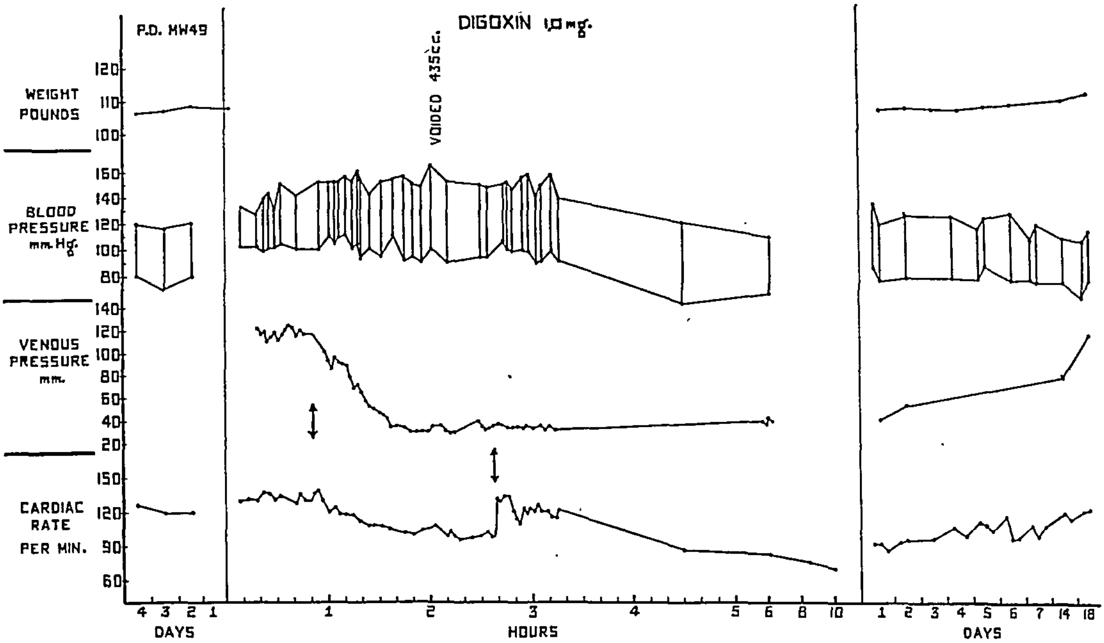

Fig. 6.—Effects produced by the intravenous injection of 1 mg. of digoxin. Mild congestive heart disease; arteriosclerotic heart disease; auricular fibrillation.

At arrow on left, patient given digoxin; at arrow on right, atropine sulfate, 2 mg. intravenously. Atropine sulfate increased the ventricular rate, but the venous pressure remained unaltered.

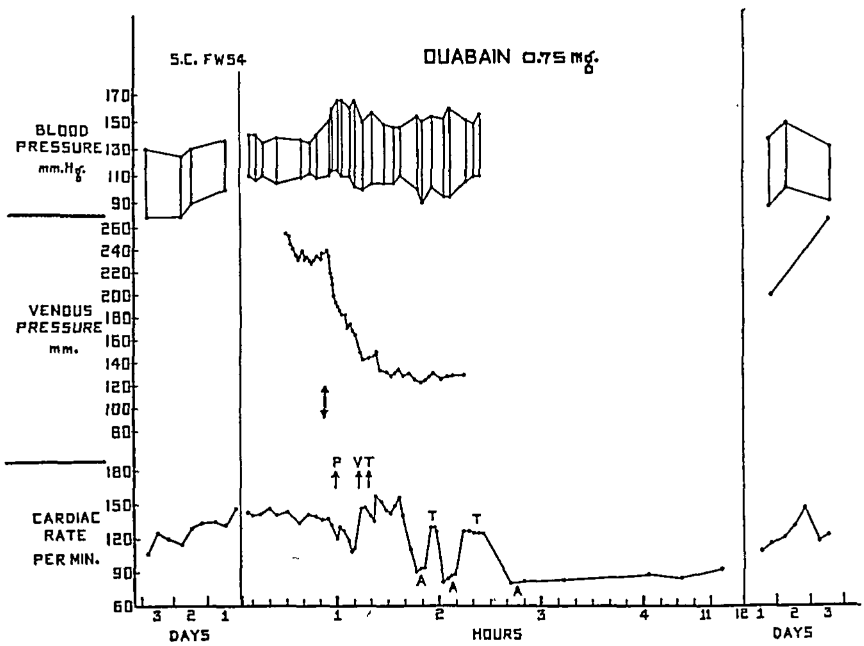

Fig. 7.—Effects produced by the intravenous injection of 0.75 mg. of ouabain. Moderately severe congestive heart disease; arteriosclerotic heart disease; auricular fibrillation.

In this case ouabain produced cardiac irregularities; at *P*, premature ventricular contractions first appeared; at *V*, they became very numerous and from varying foci. At *T*, paroxysmal tachycardia origination in the bundle of His appeared. At *A*, auricular fibrillation with a slow ventricular rate appeared.

denly ceased, and was replaced by auricular fibrillation with a normal (90 per minute) ventricular rate. During the next hour, the cardiac rhythm alternated twice between periods of His bundle tachycardia and auricular fibrillation with normal ventricular rate. The venous pressure, however, remained unchanged at its lower level (Fig. 7).

In cases of regular sinus rhythm, the dissociation between changes in venous pressure and ventricular rate was obvious; the venous pressure often fell promptly, while the ventricular rate remained unchanged (Fig. 4).

Electrocardiogram.—Excluding cardiac slowing, there was no relationship between the fall in the elevated venous pressure and the electrocardiogram.

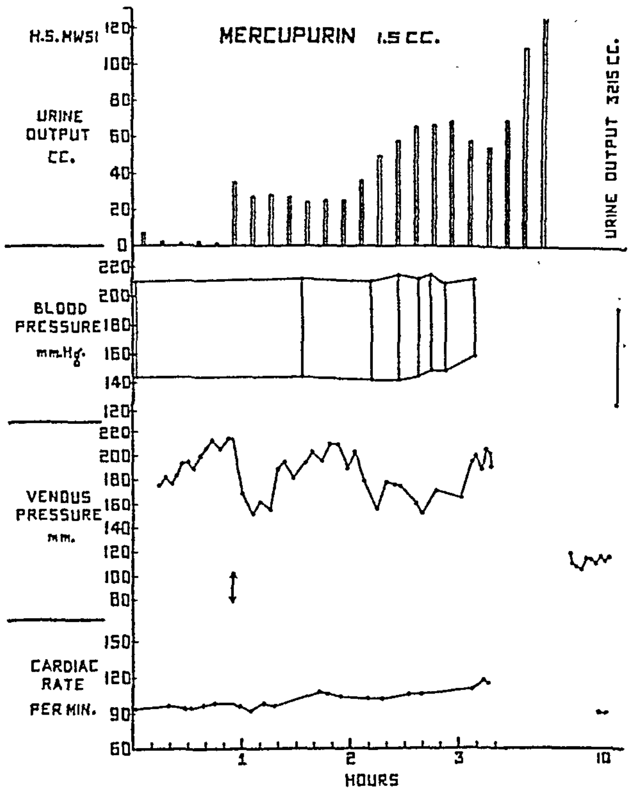

Fig. 8.—Effects produced by the intravenous injection of 1.5 c.c. of mercupurin. Severe congestive heart failure; hypertensive heart disease with regular sinus rhythm.

This patient received 1 mg. of digoxin twenty-four days previously (see Fig. 4), improved temporarily, then relapsed into severe decompensation.

Diuresis.—The rapid diuresis at times induced by the intravenous injection of the glycosides (Figs. 1 and 4) suggested the possibility that the venous pressure may have fallen as a result of a reduction in blood volume through diuresis. This is not likely. The fall in venous pressure *always* preceded the onset of diuresis (Figs. 1 and 4). Moreover, the venous pressure at times fell and no diuresis ensued (Figs. 2, 3, 5, and 7).

The venous pressure may fall when diuresis is induced by a diuretic,[2] but in that case the fall in venous pressure does not occur until after the diuresis has been initiated (Fig. 8). This is seen best when a glycoside and, after a suitable interval, a mercurial diuretic are given

to the same patient during comparable states of congestive heart failure (compare Figs. 4 and 8).

Degree of Congestive Heart Failure and Dosage.—Within the limitations imposed by the small number of injections, the *pattern* of the fall of venous pressure was the same (1) whether the initial level of venous pressure was markedly or slightly elevated (compare Figs. 2, 4, and 5 with Fig. 6 and Tables I, II, and III), (2) whether the degree of congestive heart failure was severe or mild, and (3) whether the dose was large or small, provided that it was sufficient to produce a definite effect. The magnitude of the final effect appeared to be influenced by all three of the above factors. The duration of the effect produced by a single dose of digoxin or ouabain was short, and appeared to depend on the degree of cardiac damage and cardiac reserve. If the cardiac reserve was adequate, the effect was lasting; otherwise, it was temporary. The effects produced by ouabain were usually of even shorter duration than those induced by digoxin.

DISCUSSION

When administered intravenously in single therapeutic doses, the cardiac glycosides, digoxin and ouabain, produce rapid improvement in the circulatory dynamics of patients with congestive heart failure. Most striking and constant is the rapid and considerable decrease in the elevated venous pressure. This decrease has several characteristics: It occurs without change in ventricular rate when the cardiac mechanism is normal. It is usually, but not necessarily, accompanied by a slowing of the ventricular rate when auricular fibrillation is present. It precedes the onset of diuresis. The *pattern* of the fall in venous pressure is not influenced by the initial venous pressure, the degree of the congestive heart failure, the ultimate result (recovery of compensation or temporary improvement), or the amount given, provided that a definite effect is produced. However, the magnitude of the fall and the final level of venous pressure may be affected by all of the above factors.

When compared molecule for molecule (equal, gram-molecular doses), ouabain decreases the venous pressure more rapidly than digoxin in cases of auricular fibrillation.

Because of the limited number of observations, this study cannot indicate the optimum intravenous dose of digoxin or ouabain which will induce a rapid therapeutic effect with safety. The larger doses used in this study did, at times, produce undesirable toxic effects. However, the smaller, more moderate doses induced equally striking results without complication.

Subjective improvement was noted by most patients soon after the injection of these glycosides. The rapid fall in venous pressure cannot be attributed simply to the removal of those distressing symptoms of

heart failure which artificially elevate venous pressure. Usually the fall in venous pressure preceded the onset of subjective improvement. In some patients the venous pressure fell and remained low for several hours before the distressing symptoms were relieved. The effect of the glycosides on the elevated venous pressure appears to result from an intrinsic readjustment of the circulation.

Recent investigations indicate that, during congestive heart failure, the pressure in the antecubital veins tends to approximate the pressure in the right auricle (systemic venous pressure).[3] The rapid decrease in antecubital venous pressure which we observed may well mirror a similar fall in pressure in the right auricle.

In the absence of measurements of cardiac output, the mechanism of the rapid fall in venous pressure remains unexplained. It is agreed that the cardiac output increases as the rapid ventricular rate of auricular fibrillation slows.[4] There is, however, considerable disagreement concerning the change in cardiac output during restoration of circulatory compensation when the cardiac mechanism is normal.[4] It is of interest that the elevated venous pressure decreased in a similar manner, regardless of whether the ventricular rate slowed, as in the cases of auricular fibrillation, or remained unchanged, as in cases of regular sinus rhythm.

Previous studies of the mode of action of digitalis in man have utilized oral preparations of digitalis.[5, 6] Effects were produced relatively slowly, and observations were made at long intervals of many hours to days. Data thus obtained may not permit clear recognition of primary effects and their differentiation from secondary effects. Moreover, when effects are produced slowly, they may be brought about by changes sufficiently small to be lost in the error of the methods employed.

This study has indicated a method whereby therapeutic effects are quickly achieved. Serial observations are now possible from the initiation of effects to their full establishment. This permits a more ready recognition of primary changes and their differentiation from secondary ones. Moreover, since effects are produced quickly, the changes are likely to be large and more readily recognized.

Further and more complete studies of the effects of administering glycosides intravenously may clarify the problem[5-7] of the mode of action of digitalis.

SUMMARY

1. When administered intravenously in single therapeutic doses digoxin and ouabain induced rapid improvement in the circulatory dynamics of patients with congestive heart failure.

2. A rapid fall of the elevated venous pressure was the most striking and constant effect produced. It had the following characteristics:

a. Onset of effect: ouabain, 3 to 11 minutes, digoxin, 5 to 22 minutes

b. Major effect: ouabain, 35 to 56 minutes, digoxin, 45 minutes to 3 hours.

c. It was associated with, but not dependent on, slowing of the ventricular rate when the cardiac mechanism was auricular fibrillation.

d. It was unaccompanied by a change in ventricular rate when the cardiac mechanism was normal.

e. It preceded the onset of diuresis, which at times was rapidly initiated.

f. Its pattern did not depend on the initial level of venous pressure or the degree of congestive heart failure.

g. It bore no relationship to changes in the electrocardiogram.

h. Its duration was relatively short, except in those patients whose cardiac reserve was sufficient to maintain circulatory compensation once it was re-established.

3. Compared molecule for molecule, ouabain induced effects more rapidly than digoxin.

4. Large doses of these two glycosides at times induced toxic complications. The intermediate doses were free of these effects and therapeutically just as effective.

The authors are indebted to Dr. Arthur C. DeGraff for his helpful advice and criticism throughout this study. The Misses Helen Pomykala and Bertha Rader assisted in this work.

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FURTHER OBSERVATIONS ON THE ISCHEMIA-INJURY PATTERN PRODUCED IN THE DOG BY TEMPORARY OCCLUSION OF A CORONARY ARTERY. INCOMPLETE T DIVERSION PATTERNS, THEOPHYLLINE T REVERSION, AND THEOPHYLLINE CONVERSION OF THE NEGATIVE T PATTERN

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IN A preliminary communication,[1] a method was described for observing the electrocardiographic evolution of the development and cessation of acute local ventricular ischemia and injury. Continuous recordings were made before, during, and after a sudden, complete, brief occlusion of the anterior descending branch of the dog's left coronary artery. Since the indifferent electrode was on the left foreleg and the exploring electrode was in contact with the anterior surface of the pericardial sac (close to the heart), the lead was regarded as essentially unipolar.[2] The sequence of changes observed was called the positive T pattern or the negative T pattern, according to the form of T in the control recorded after dissection of the artery and before occlusion. In each pattern variety the form of T returned to the form of the preocclusion control within several minutes or less from the time occlusion ended.[1]

In general, the ischemia-injury pattern displays two features of fundamental importance. First, its sequential changes resemble in all essential particulars the much more lengthy sequence of temporary changes encountered during the course of myocardial infarction, and thereby demonstrate that homologous changes associated with infarction (which are produced by muscle undergoing similar physiologic changes) are independent of, and not necessarily diagnostic of, myocardial infarction. Second, the ischemia-injury pattern shows (contrary to general opinion) that the first stage in the electrocardiographic evolution of myocardial infarction is the appearance of *primary T-wave changes which are* ascribed to local ventricular ischemia.[1, 3, 4]

INCOMPLETE T DIVERSION PATTERNS

The expression "diversion of T" refers to a change in the form of T in a direction away from the normal (or control), whereas "reversion of T" refers to a change from the abnormal back toward the normal

Presented at the meeting of the Southern Section of the Society for Experimental Biology and Medicine, June 25, 1943.
Received for publication April 6, 1943.

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(or control) form. Hence, the T-wave changes which begin a few seconds after the onset of occlusion and continue for a fraction of a second after cessation of occlusion represent diversion changes. During a 90-second period of occlusion, ischemia produces a local negative diversion of T, and injury subsequently produces a local positive diversion of T.[1] It is desirable to know how far these diversions progress when occlusion is suddenly discontinued during the developmental period. Strips *c, d, e, f,* and *g* (Fig 1) are from a continuous recording before, during, and

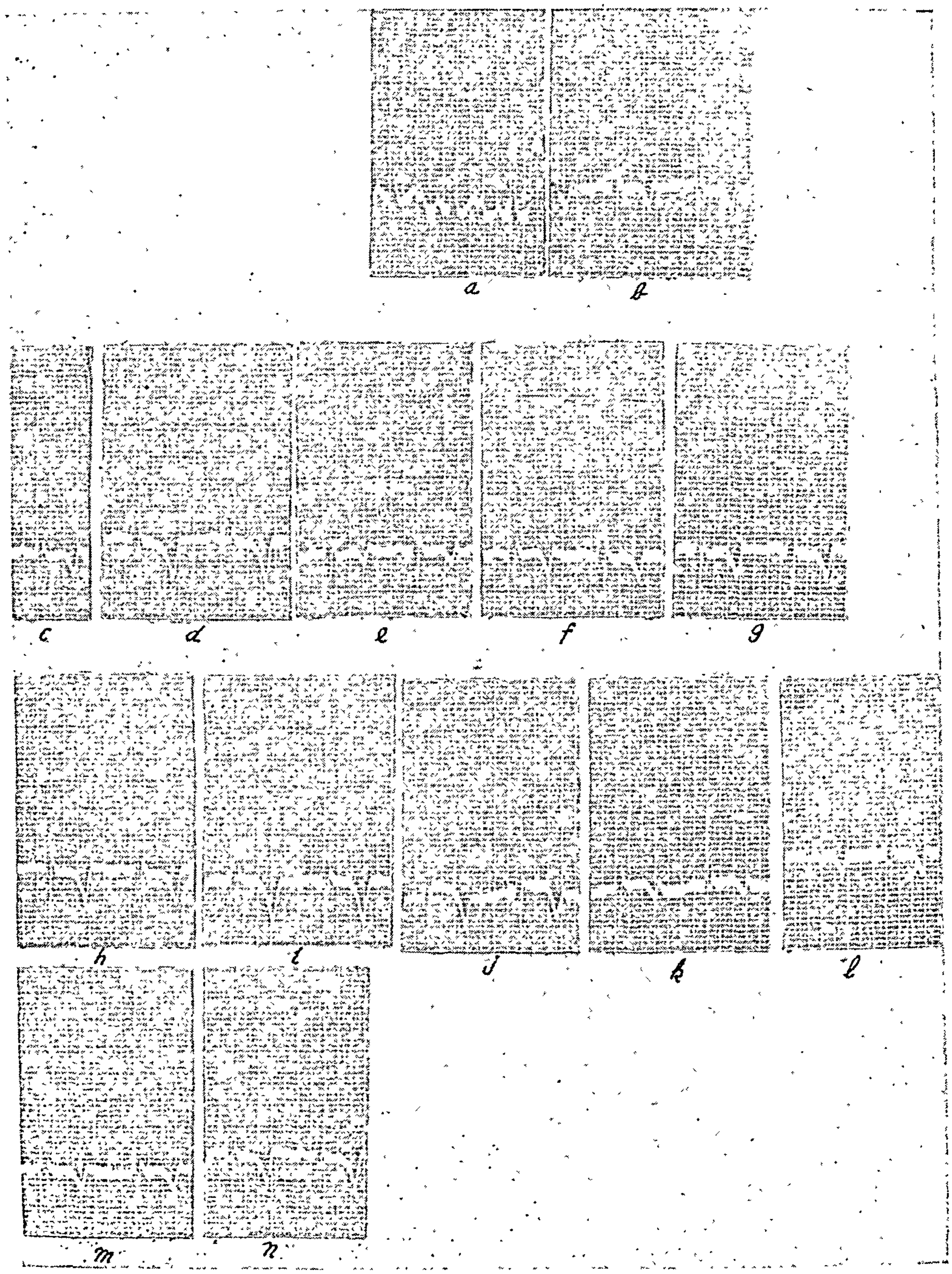

Fig. 1.—Strips *a* and *b* are from control curves, made before and after arterial dissection. Strips *c, d, e, f,* and *g* are from a continuous curve made before, during, and after a 30-second occlusion. Strips *h, i, j, k, l, m,* and *n* are from a continuous curve made before, during, and after a 45-second occlusion. See text.

after a 30-second occlusion. The occlusion commenced between strips *c* and *d* and ended between strips *e* and *f*. No definite injury shifts developed. The occlusion was promptly repeated and maintained until the recorder judged (by watching the shadow of the galvanometer string) that the injury effect had just begun to develop, whereupon the occlusion was promptly terminated. Strips *h*, *i*, *j*, *k*, *l*, *m*, and *n* (Fig. 1) show the maximal developments which occurred. Occlusion started between strips *h* and *i* and ended 45 seconds later, immediately after strip *k*. Evidentially, the ischemia-injury pattern may be promptly arrested during its development at any arbitrary stage by sudden termination of occlusion, after which the pattern promptly reverts to its control form.

THEOPHYLLINE REVERSION OF THE NEGATIVE T PATTERN

Control curves recorded immediately before and after dissection of the coronary artery are shown in Fig. 1, *a* and *b*. A negative T pattern recorded from the animal before, during, and after a 90-second occlusion has been described elsewhere.[1] As the intravenous administration of 0.12 Gm. of theophylline with ethylene diamine was completed, the continuous recording shown in Fig. 2 was commenced. The T deflection is reverted from a negative into a positive deflection within 60 seconds. The reversion is not complete, however, for the initial T segment continues to make a rounded negative dip. The manner of the T reversion is such that the descending limb of the inverted spike, together with the base of its ascending limb, moves upwards, producing an M deflection in the hemireversion stage. In the final stage of reversion, the remainder of the spike forms a shallow notch in the ascending limb of the reverted T. We have been able to repeat the theophylline T reversion on two subsequent occasions. Evidentially, dissection of the artery is occasionally followed by a relatively steady arteriolar spasm throughout its terminals, and theophylline with ethylene diamine promptly relaxes the spasm and subtotally abolishes the associated ischemia.

THEOPHYLLINE CONVERSION OF THE NEGATIVE T PATTERN

Immediately after the drug-induced reversion of T (shown in Fig. 2), a continuous curve was made before, during, and after a 90-second occlusion. Strips from the critical stages of the pattern are shown in Fig. 3. Observation of the galvanometer movements during the experiment clearly indicated that the evolution of the pattern had been altered profoundly. The maximal ischemia effect is shown in strip *d*, and the maximal injury effect is shown in strip *f*. The effects produced are like in kind, but of diminished magnitude when compared with homologous strips recorded from the same preparation under similar circumstances before administration of the drug. The 90-second post-theophylline occlusion was repeated ten minutes later after a second

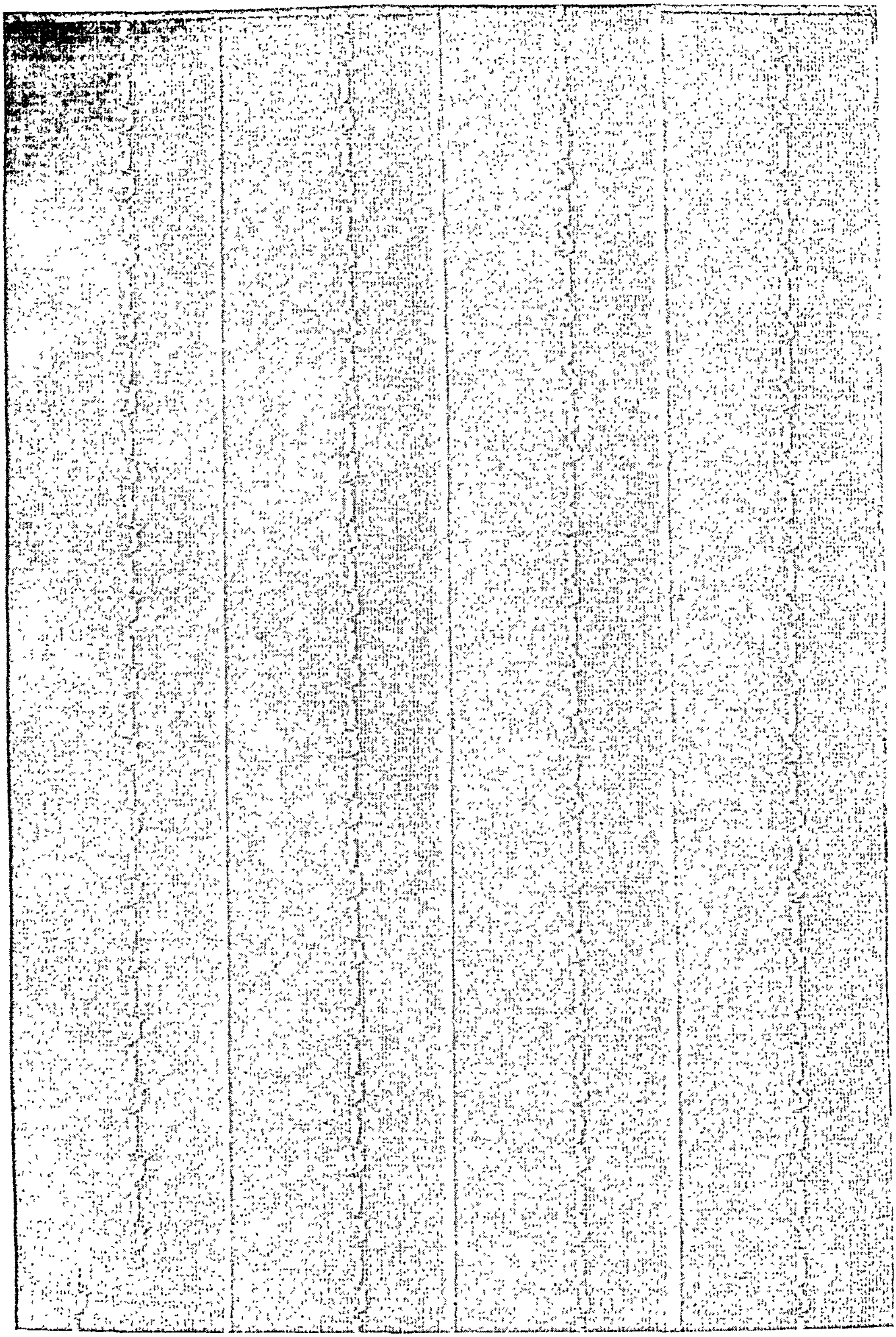

Fig. 2.—A continuous strip, showing the theophylline T reversion. See text. Read from left to right and from above downward.

similar dose. The complete pattern (reading from left to right and from above downward) is shown in Figs. 4 and 5. Here, the effect ascribed to ischemia (strips 2 and 3) is somewhat more pronounced, and the effect ascribed to injury (strips 4 through 8) reaches a maximum (strip 7) comparable to that shown by the homologous strip of the pretheophylline occlusion. The T deflections in Figs. 4 and 5 are positive just before occlusion begins, and remain positive after occlusion terminates. Evidentially, ischemia-injury patterns which are

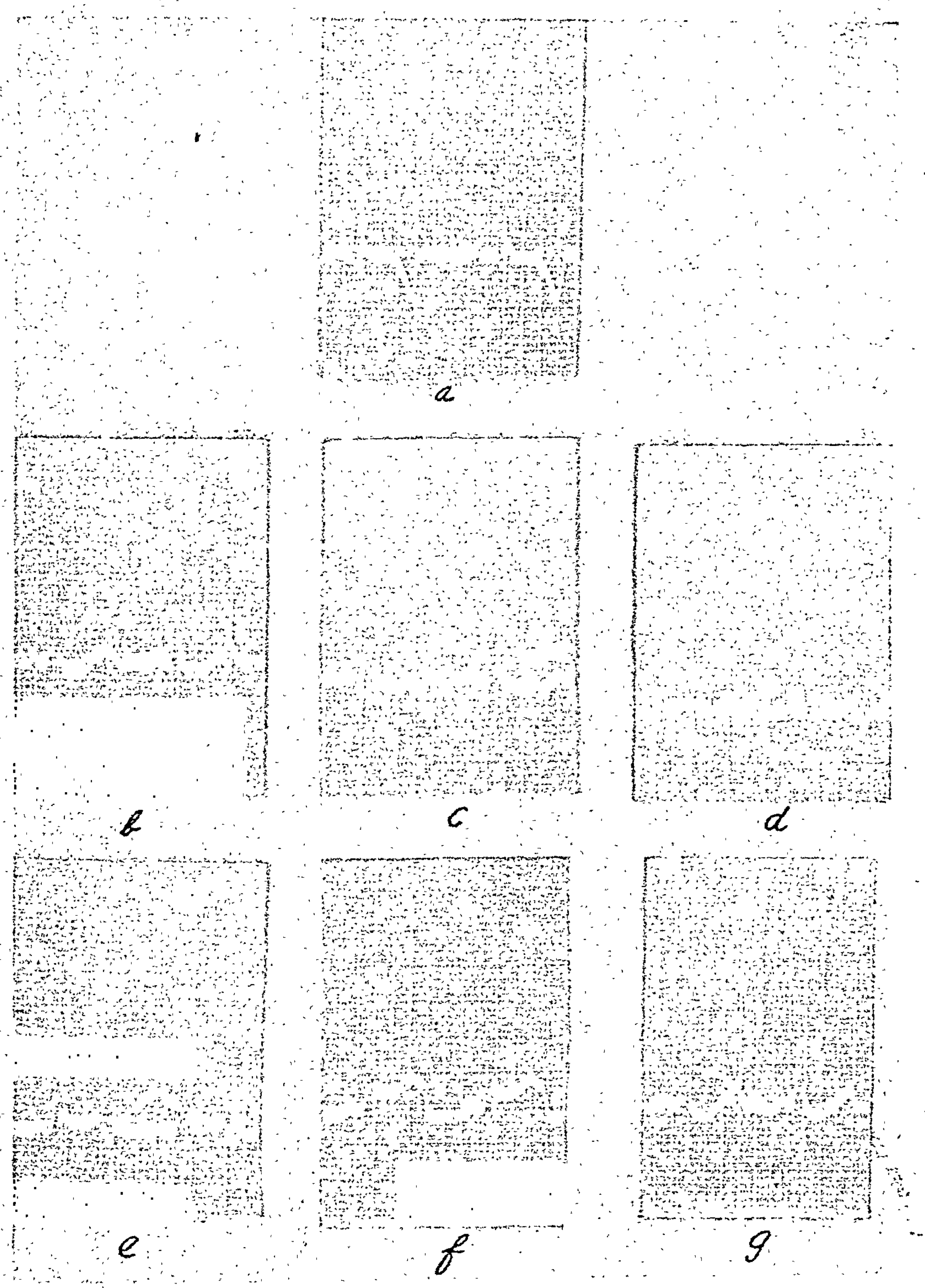

Fig. 3.—Strips from a continuous curve made before, during, and after a 90-second posttheophylline occlusion. See text.

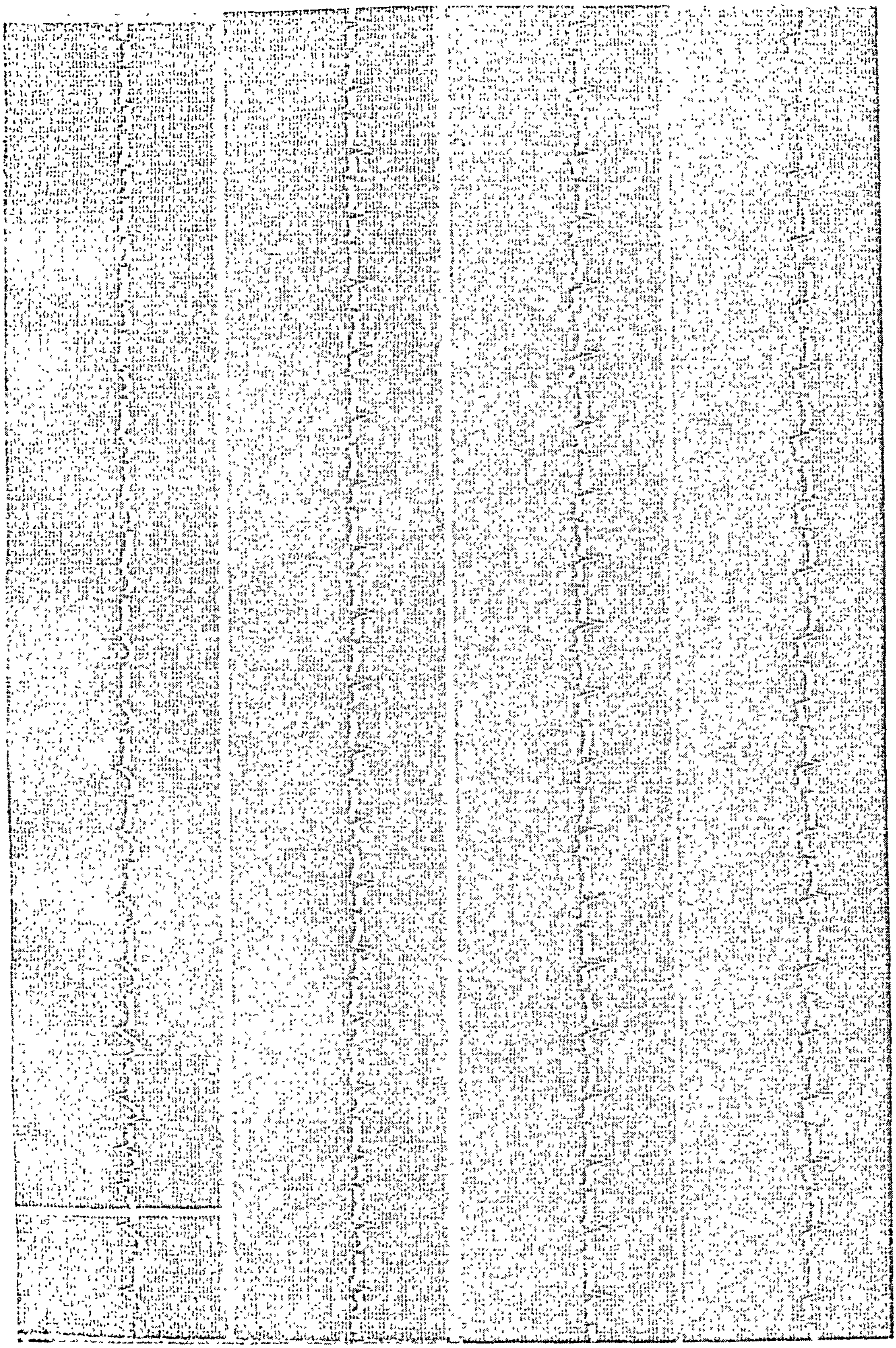

Fig. 4.—Reading from left to right and from above downward and continued in Fig. 5, a continuous strip made before, during, and after a posttheophylline occlusion. See text.

initially of the negative T variety may be converted by theophylline into patterns of the positive T variety.

THE LOCAL CHARACTER OF THE EFFECTS

Since our preliminary communication,[1] we have carried out ten occlusion experiments on three dogs with the idea of demonstrating the strictly local character of the muscle changes induced by occlusion.

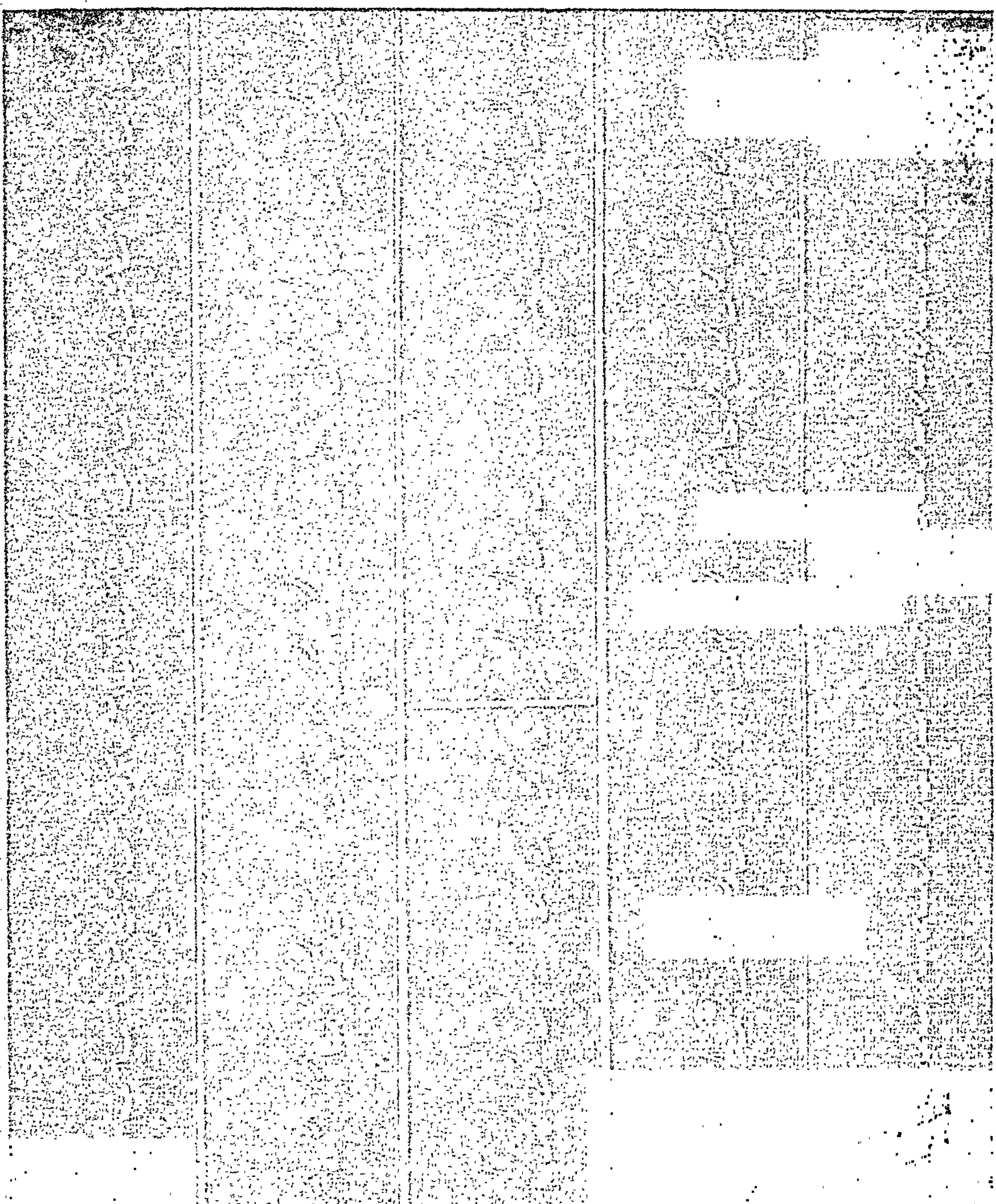

Fig. 5.—Strips of a continuous curve showing a continuation of the effects commenced in Fig. 4. See legend of Fig. 4 and text. Time lines in all curves are 1/10 second apart. Standardization in all curves is approximately 2/3 normal.

In all ten experiments, two essentially unipolar leads were recorded simultaneously by a two-string galvanometer of the Einthoven type. In nine of the occlusion experiments, one of the exploring electrodes was placed on the subcutaneous tissues of the right hemithorax immediately superficial to the apex impulse of the right ventricle. The

other exploring electrode was placed (as usual) in contact with the anterior surface of the pericardial sac superjacent to the free wall of the left ventricle. The two indifferent electrodes were contacted with the subcutaneous tissue of the left foreleg. With one exception, the effects produced by the apex of the right ventricle were of a minor kind, and consisted of an upward peaking of the T deflection concurrent with the injury effect from the left ventricle. In the exceptional experiment, the curve written by the left ventricle was of the negative T variety, whereas the simultaneous curve written by the apex of the right ventricle displayed definite injury effects. The preparation which yielded the exceptional patterns was promptly treated with an intravenous injection of 0.12 Gm. of theophylline. A T reversion immediately occurred in the curve recorded from the right ventricle, but failed to appear in the curve recorded from the left ventricle. Moreover, subsequent occlusion patterns recorded from the left ventricle continued to be of the negative T variety. However, they were associated with a total absence of all injury effects in curves recorded simultaneously from the right ventricle. The remaining occlusion experiment, conducted with two simultaneous recordings, was carried out in the usual way except for the position of the exploring electrode superjacent to the apex of the right ventricle. The electrode was moved to a subcutaneous position superjacent to the electrode on the pericardial sac. The two occlusion patterns thus obtained closely resembled one another. As a result of these observations we see no reason for doubting that the muscle changes responsible for the ischemia-injury pattern are strictly local. The characteristics of the pattern are due to altered physiologic processes in that region of the myocardium which is ordinarily irrigated by the occluded artery.

COMMENTS

If it is assumed that dissection of a dog's coronary artery may, in some instances, induce a relatively steady local ischemia, the occurrence after dissection of a negative T rather than a positive T is explained. The fact that theophylline with ethylene diamine usually reverts the negative T suggests that the assumed local ischemia may be the result of a relatively steady arteriolar spasm throughout the terminals of the dissected artery. We have noted that the more difficult and traumatizing dissections have been attended with inversion of the T deflection. During dissection, every effort is made to avoid arterial compression. After dissection, experimentation has not been delayed to ascertain whether spontaneous T reversion ultimately occurs. There appear to be no essential differences in the positive T, as compared with the negative T, patterns. The latter appears to evolve (when occlusion begins) from a steady state of low-grade ischemia, to which the evolution reverts when occlusion ends.

The changes in the ischemia-injury pattern which are encountered after the administration of theophylline with ethylene diamine indicate that the drug is capable of reducing the intensity and (or) extent of local ischemia and injury by enhancing the collateral circulation of the involved region. The evidence, such as it is, might be interpreted as supporting the opinion of Fowler, Hurevitz, and Smith[5] that theophylline with ethylene diamine is capable of reducing the extent of myocardial infarction.

A satisfactory theory concerning the evolution of ischemia and injury and the relationship of these changes to myocardial infarction in man has been advanced by one of us.[4] At present we see no reason for altering these concepts when applying the theory to the electrocardiographic evolution of myocardial infarction in the dog. On the other hand, the results of our present experiments, which deal with ischemia and injury, and which are strictly comparable only to the initial electrical stages of infarction, lend considerable support to the theoretical concepts.

If the duration of the T diversion pattern of acute local ventricular ischemia was always as brief (30 to 40 seconds) as the patterns demonstrate, a like occurrence in man would be of academic interest only. Certain clinical observations suggest that such is not the case.[3, 4] In this connection it is to be remembered that the ischemia-injury patterns which we observed were produced by sudden, complete occlusion. Experimental evidence is now in hand which suggests that the development of the ischemia phase (negative T diversion) of the pattern can be arrested and maintained at any desired stage for prolonged periods by varying the amount and duration of *subtotal* occlusion. We hope to deal more fully with this phase of the problem in a subsequent report.

SUMMARY

1. The ischemia-injury pattern, although produced by sudden, complete, brief occlusion of a coronary artery, is in no way dependent upon the presence of myocardial infarction. However, the pattern demonstrates the early electrocardiographic changes which may be encountered before and during the early development of myocardial infarction. Contrary to general opinion, the first electrocardiographic change is a primary T-wave change ascribed to acute local ventricular ischemia.

2. The diversion stages of the pattern may be arbitrarily interrupted by terminating the occlusion, whereupon reversion of the pattern promptly occurs.

3. The negative T diversion induced by dissection of the coronary artery can frequently be reverted by an intravenous administration of 0.12 Gm. of theophylline with ethylene diamine.

4. After the theophylline T reversion, the ischemia-injury pattern, which was formerly of the negative T variety, is converted in all essential particulars to a pattern of the positive T variety.

5. Evidence is presented which indicates that the ischemia-injury pattern owes its characteristics to acute local changes in that region of the ventricular wall which is subjacent to the exploring electrode, a region ordinarily irrigated by the occluded artery.

6. An explanation is offered for the occurrence of two typical patterns rather than one.

7. Certain electrocardiographic changes are observed after the administration of theophylline with ethylene diamine, and are ascribed to a decrease in the intensity and (or) extent of local ischemia and injury, a decrease produced by improvement of the collateral circulation.

8. The clinical significance of the ischemia-injury pattern and of its behavior under varied circumstances is briefly discussed.

Thanks are expressed to Dr. S. A. Romano, of the Department of Surgery, for considerable help and advice in the surgical aspects of the work. Thanks are also expressed to J. C. Williamson and to Mrs. M. E. Bayley, R.N., for technical assistance.

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PERSISTENT DISPLACEMENT OF THE RS-T SEGMENT IN A CASE OF METASTATIC TUMOR OF THE HEART

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TUMORS of the heart and pericardium have aroused considerable interest, if one may judge from the large number of cases that have been reported. In several instances the correct diagnosis has been made ante mortem.[1-5] There are also several extensive reviews of the literature[6-8] which present data on many examples of both primary and secondary cardiac neoplasm. It is our present purpose to describe a patient with carcinoma of the esophagus which involved the heart and produced very unusual electrocardiographic abnormalities. The frequency of cardiac invasion in various neoplastic diseases is reported to range from 2.0 per cent[9] to 10.9 per cent.[10] Three different mechanisms leading to involvement of the heart are mentioned: (a) embolic metastases via the coronary arteries, (b) invasion through the lymphatic channels, and (c) direct extension from either a primary or secondary tumor in the lung or mediastinum. Metastases to the heart or pericardium have been observed in association with malignant tumors arising in many different organs, and carcinoma of the esophagus frequently involves these structures.

CASE REPORT

History.—J. K., Reg. No. 496456, a 53-year-old Austrian, was admitted to the University Hospital Jan. 14, 1942, complaining of progressive difficulty in swallowing over a period of two months. He had developed nausea and vomiting of undigested food shortly after eating, and for three days he had been unable to eat at all. There was an almost constant, dull ache and sense of fullness beneath the xiphoid process, aggravated by taking food. The resulting loss of weight amounted to 30 pounds (13.8 kg.). The past history and family history were essentially negative.

Physical Examination.—The patient appeared chronically ill and was obviously emaciated. The temperature, pulse rate, and respiratory rate were normal. The heart was normal in size, the cardiac sounds were normal in character, and no murmurs were heard. The blood pressure was 130/90. A few crepitant râles were present at both lung bases posteriorly. The remainder of the examination revealed no abnormalities.

Laboratory Examinations.—The blood Kahn reaction was negative. Examination of the blood disclosed a hemoglobin content of 90 per cent

This study was aided by a grant made to Dr. F. N. Wilson by the Horace H. Rackham School of Graduate Studies.

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Received for publication May 3, 1943.

(Sahli) and 8,000 leucocytes per cubic millimeter. On admission the urine showed 8 to 10 leucocytes per high power field, but six days later it was negative. The total protein content and the chloride content of the blood were normal.

Roentgenographic Examinations.—Roentgenographic studies of the upper gastrointestinal tract revealed a carcinoma of the lower third of the esophagus. Roentgenograms of the thorax showed no evidence of metastases, and the heart was normal in size and shape.

Clinical Course.—An esophagoscopy was performed Jan. 19, 1942. A polypoid, pendunculated lesion, almost filling the esophageal lumen, was encountered 32 cm. from the teeth. Biopsy of this mass revealed a squamous-cell carcinoma.

During the following eleven months a series of surgical procedures was carried out for the purpose of removing the tumor and reconstructing the upper gastrointestinal tract (Drs. C. Haight and E. B. Kay). On January 28, a Beck-Jainu tube was constructed along the greater curvature of the stomach and the spleen was removed. On February 12, the esophagus was mobilized throughout its length and brought out through an incision in the neck, the tumor was resected, and a cervical esophagostomy was created. The neoplasm proved to be a cornifying squamous-cell carcinoma, grade II, with extensive infiltration of the periesophageal fibroadipose tissue and skeletal muscle. On February 24, a gastrostomy was performed, and the Beck-Jainu tube was brought out over the costal arch. Soon thereafter the patient was able to eat a soft diet by connecting the esophageal with the gastric stoma by means of a rubber tube. On May 28 and October 22, reconstructive plastic procedures upon the gastric stoma were done. On December 8, the first stage of an esophagoplasty to create an anterior thoracic esophagus was performed.

On December 15, a trigeminal pulse was noted and an electrocardiogram was ordered. On the following day, while being taken to the Heart Station in a wheel chair, the patient experienced a sudden, severe pain in the precordium with radiation to the left arm, lasting about ten minutes. While moving from the chair to a bed, before the tracing was made, he felt faint and there was momentary loss of consciousness. As soon as he assumed the supine position he was relieved of all symptoms. The electrocardiogram showed prominent Q waves, marked upward displacement of the RS-T segment, and terminal inversion of the T waves in Leads II and III and Lead V_F (Fig. 1*A*). Examination of the heart on the following day showed no abnormalities; the blood pressure was 98/82. There were no significant changes in the temperature, pulse, or respiration, and, with the exception of slight, dull, precordial discomfort for a few days, no further symptoms. Treatment for acute myocardial infarction was instituted.

After this incident the patient did not regain his strength and became increasingly difficult to manage. It was frequently necessary to supplement gastrostomy feedings with fluids parenterally. On December 21, the blood nonprotein nitrogen was 68.5 mg. per cent, and examination of the urine showed albumin (1 plus), 8 to 10 leucocytes per high power field, and two to three hyaline and granular casts per low power field.

Early in January, 1943, the patient began to complain of dull pain in the lower left part of the chest anteriorly, and in the axilla. This was present intermittently thereafter until his death. Roentgenographic

examination of the chest on January 27 showed a bizarre protuberance along the lower left cardiac border and at the apex, which gave the heart a boot-shaped ("coeur en sabot") outline.

On Feb. 16, 1943, the patient was allowed up in a chair for the first time after his attack of pain in December. At this time his mental status was much improved and he took liquid nourishment well. Two days later, however, he had a sudden attack of pain in the *precordium*, associated with cyanosis, shallow respirations, and loss of consciousness for about one minute. The blood pressure fell within the next 24 hours to 76/40, but after 48 hours it rose to 90/60. Examination of the heart revealed a gross cardiac irregularity, but no other significant changes from previous findings. Except for persistence of occasional, dull pain

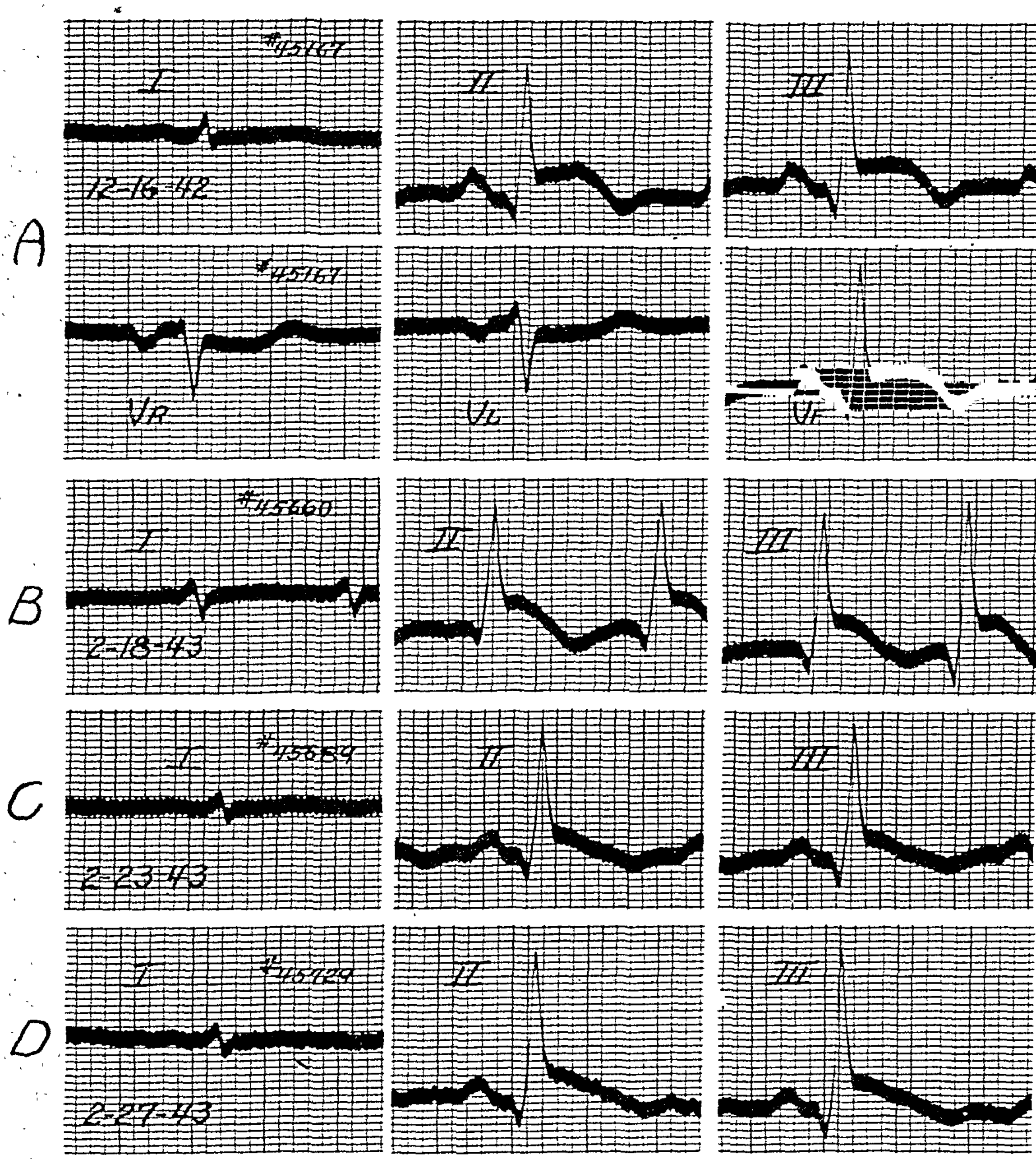

Fig. 1.—*A*. Standard leads and extremity potentials on Dec. 16, 1942. Note prominent Q waves, elevation of the RS-T segment, and terminal inversion of the T wave in Leads II, III, and Vr.

B. Standard leads on Feb. 18, 1943. RS-T displacement is present and auricular fibrillation has appeared.

C. Standard leads on Feb. 23, 1943. Normal sinus rhythm now present.

D. Standard leads on Feb. 28, 1943, show persistent RS-T displacement.

in the left lower anterior and lateral chest region, all symptoms quickly disappeared.

The electrocardiograms taken Feb. 18, 1943, immediately after this attack, show auricular fibrillation with a ventricular rate of 150 per minute. There is pronounced upward displacement of the RS-T segment in Leads II and III (Fig. 1*B*) and V_F, such as occurs in fresh posterior infarction. In this respect these tracings are much like those taken Dec. 16, 1942. Similar, but even more striking, displacement of the RS-T segment is present in several of the unipolar precordial leads;

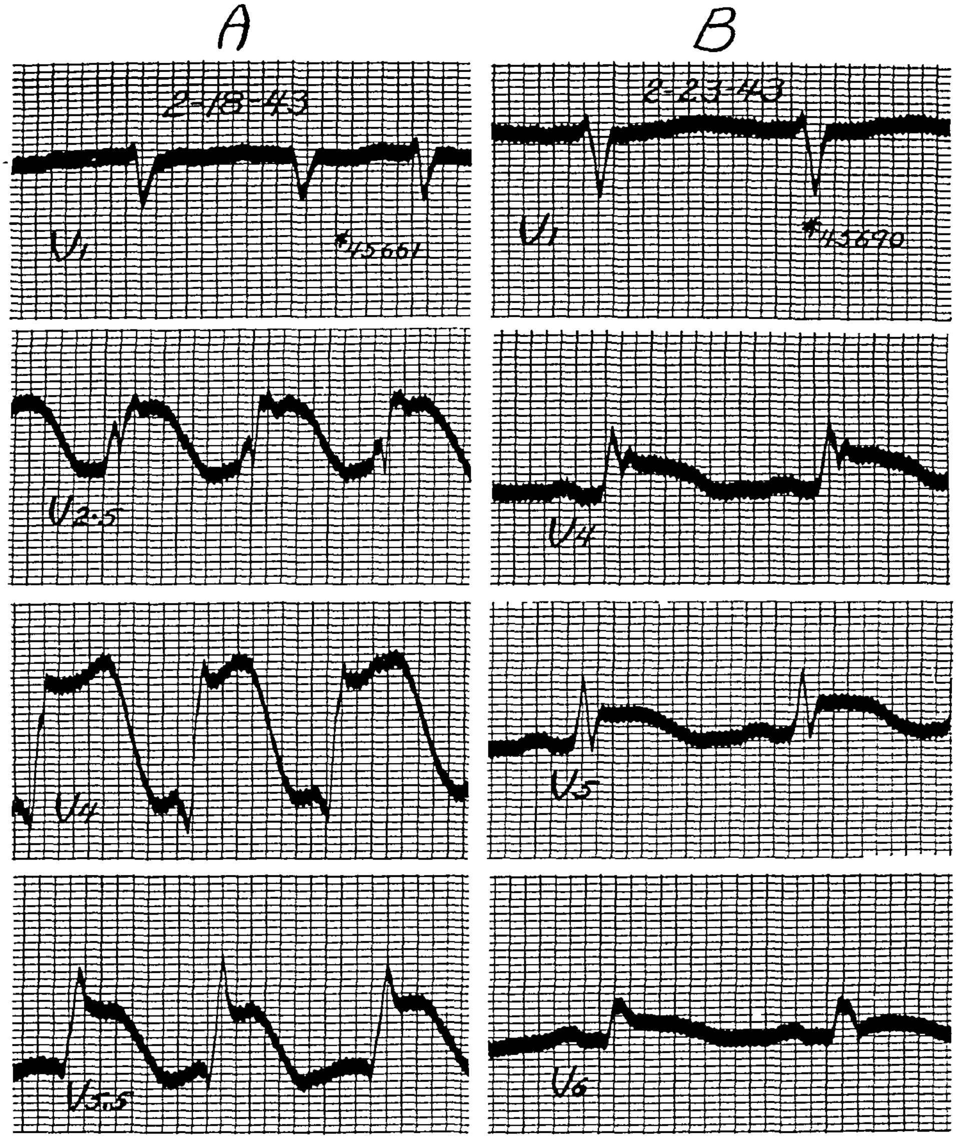

Fig. 2.—*A*. Unipolar precordial leads on Feb. 18, 1943. Note striking elevation of RS-T segment in all leads taken from points to the left of the sternum. Leads could not be taken from the usual six precordial points because of the operative wounds and dressings $V_{2.5}$ and $V_{5.5}$ represent leads from points midway between V_2 and V_3, and V_5 and V_6 respectively.

B. Unipolar precordial leads on Feb. 23, 1943. RS-T displacement still present, although less conspicuous.

this change is more characteristic of a very recent anterior myocardial infarction (Fig. 2*A*). The standard and precordial curves taken five days later (Figs. 1*C* and 2*B*) are essentially the same, except that the RS-T displacement in the latter is somewhat less conspicuous and normal rhythm is present. The standard leads taken ten days after the

second attack of pain show persistent displacement of the RS-T segment in Leads II and III (Fig. 1*D*).

The patient became progressively more depressed, unruly, and lethargic. He had a moderately productive cough, but exhibited no other manifestations of congestive heart failure. On March 3, the blood pressure was 88/58. On the following day his condition was not greatly changed until midday, when he was found unconscious in his bed. He had Cheyne-Stokes respiration and the pulse was imperceptible. He died within a few minutes.

Post-mortem Examination (Performed by Dr. W. A. Stryker).—The heart appeared to be a firm, white mass of neoplastic tissue; it weighed 550 grams. The entire apical portion was replaced by carcinomatous

A. *B.* *C.*

Fig. 3.—Tranverse sections of the heart, showing extensive neoplastic invasion.
A. From midportion; cavity of left ventricle and normal myocardium seen above.
B. From point midway between *A* and *C.*
C. From cardiac apex.

Fig. 4.—Microphotograph of section of heart. At points *A*, myocardium shows necrosis and atrophy. Infiltrating neoplasm is seen at points *B*. Stroma of neoplasm shown at *C*.

tissue in which there were small foci of necrosis. In the middle portion there was carcinomatous replacement of the lateral and posterior aspects of the left ventricle, the interventricular septum, and nearly all of the right ventricle, so that the only normal appearing myocardium was that of the anterior wall of the left ventricle adjacent to the interventricular septum (Fig. 3). The neoplasm extended to within 2 cm. of the aortic ring, and involved the papillary muscles, as well as the chordae tendineae, of the mitral valve. The auricles and all valve cusps were essentially normal. The anterior descending branch of the left coronary artery could be identified throughout one-half its course; it showed only slight atherosclerosis. Metastases were present in the mediastinal, tracheobronchial and peripancreatic lymph nodes, the liver, the right kidney, and both lungs.

Microscopic study of the heart revealed a metastatic, heavily cornifying, squamous-cell carcinoma (Fig. 4). The myocardium showed focal areas of necrosis and atrophy, as well as patchy interstitial fibrosis. Serous atrophy of adipose tissue and focal aggregations of lymphocytes were present in the epicardium. The neoplasm displayed necrosis, with surrounding polymorphonuclear and foreign-body giant-cell reaction. There was an adhesive fibrous pericarditis, but no evidence of direct extension of the neoplasm in the mediastinum to the myocardium was found.

DISCUSSION

The electrocardiographic abnormalities that occur in tumor of the heart are in no way distinctive, and depend upon the location of the neoplasm.[10, 11] Right bundle branch block has been described in patients with involvement of the interventricular septum[1-3]; partial heart block[12] and complete atrioventricular block[13] have been observed when the region of the atrioventricular node and His bundle has been affected; and tumors extending into the cavity of the right auricle have been accompanied by significant changes in the P waves.[14] Paroxysmal auricular flutter, atrioventricular nodal rhythm, or paroxysmal auricular fibrillation, which occurred in our patient, have been reported frequently,[2, 4, 5, 15] but have not proved very helpful in locating the neoplasm. Electrocardiograms characterized by small QRS complexes in all leads have also been recorded, but are of little value in diagnosis because they occur in a variety of conditions.[5, 8]

Inversion of the T wave of the type usually seen in acute myocardial infarction occurred in three of the previously reported cases of primary or secondary neoplasms of the heart or pericardium. In none of them was it accompanied by characteristic alterations of the QRS complex. In the case described by Boman[16] there was slight elevation of the RS-T segment over a period of twenty-nine days. The patient was found to have a primary sarcoma of the pericardium, with only superficial infiltration of the myocardium. Pronounced and persistent RS-T displacement comparable to that observed in the case reported here has not been described heretofore in any case of cardiac neoplasm. Barnes and his co-workers[17] have stated that such an elevation of the level of the

take-off of the RS-T segment is not to be anticipated from tumorous invasion of the left ventricle.

Strong evidence supports the view that RS-T displacement is the result of acute myocardial injury, whether produced by general anoxemia,[18] by vasospastic drugs,[19] by acute pericarditis,[20] by physical or chemical means,[21] or by coronary arterial vasospasm[22] or occlusion with resulting ischemia.[23] Mechanical or thermal injury to the subepicardial ventricular muscle produces RS-T displacement which persists for about thirty minutes. The displacement subsides either because the injured muscle dies or because new cell membranes are formed by protoplasmic condensation. When the agent producing the injury acts over a longer period, it may continue much longer. In coronary occlusion it seldom lasts for more than a few days, but in rare instances it may persist for weeks or months. On the basis of our present knowledge it seems logical to attribute long-continued RS-T displacement to maintained or repeated injury which prevents the formation of new cell membranes or continuously spreads to previously unaffected muscle. Nevertheless, this explanation of persistent RS-T displacement seems incompatible with the history of uninterrupted recovery in some of the cases of myocardial infarction in which it is observed. In two cases of this kind which have come to our notice, myocardial infarction was followed by the development of an aneurysm of the left ventricle,[24] but the association of ventricular aneurysm and persistent RS-T displacement may have been a coincidence. Because of these previous observations, aneurysm of the left ventricle was suspected in the present case because of the long-lasting RS-T displacement and the changes in the contour of the cardiac silhouette, as demonstrated by serial roentgenograms. Neoplastic invasion of the heart was also considered, but it seemed doubtful that it could explain the unusual electrocardiographic changes.

The persistent elevation of the RS-T segment in our patient might conceivably be accounted for in several ways: (a) constant or intermittent compression of one or more of the coronary arteries by the large tumor mass, with resultant myocardial ischemia, (b) direct extension into the lumina of the coronary arteries, or coronary embolism due to fragments of the tumor, (c) neoplastic invasion of the pericardium acting in the same way as other forms of pericarditis, or (d) almost continuous myocardial injury by pressure or by physicochemical action, or by interference with the blood supply as the malignant tissue invaded the heart. The microscopic observations (Fig. 4) tend to support this last hypothesis.

A puzzling feature of the electrocardiograms taken after the second attack of pain was the association of changes in Leads II and III that suggested a recent posterior myocardial infarct (Fig. 1*B*) with changes in the precordial leads, taken at the same time, which were characteristic

of fresh anterior infarction (Fig. 2A). Simultaneous, acute anterior and acute posterior infarction can occur but is certainly unusual. A large anterior infarct involving the cardiac apex in a person with a vertically placed heart could theoretically explain the electrocardiographic changes and could account for the resemblance of the potential variations of the left leg (V_F) to those that occur at the epicardial surface of an infarct. At the post-mortem examination the distribution of the neoplasm, which involved the anterior, apical, and posterior walls of the left ventricle, satisfactorily explained the simultaneous presence of upward RS-T displacement in the chest leads and in Leads II and III.

In view of the massiveness of the cardiac tumor at autopsy, the absence of congestive cardiac failure during life is surprising. The failure of extensive neoplastic invasion of the heart to induce cardiac failure has been noted repeatedly,[6, 13, 25, 26] and is felt to be particularly characteristic of metastatic tumors of the heart. Other instances of practically complete replacement of the heart by metastatic carcinoma, accompanied by surprisingly few or mild symptoms, have been reported.[27, 28] Precordial pain was the most significant symptom experienced by our patient. It was not characteristic of angina pectoris in many respects. Yater[6] and Lisa, et al.,[8] have pointed out that anginal attacks are common in patients with cardiac tumors. One of the patients observed by Fishberg[2] was in status anginosus for sixteen days; the autopsy disclosed a mass of tumor surrounding and constricting the circumflex branch of the left coronary artery. This was considered a possible explanation of the pain. In the cases described by Auerbach, et al.,[15] and Boman[16] there was also discomfort suggestive of angina pectoris, but in both of these instances the cause was probably neoplastic invasion of the pericardium. The distress experienced by the patient reported here may have resulted from myocardial ischemia due to interference with the coronary arterial flow, from invasion of the cardiac nerves or other mediastinal structures, or from the associated pericarditis.

SUMMARY

A case of carcinoma of the esophagus with massive metastases to the heart is reported. Serial electrocardiograms displayed persistent upward displacement of the RS-T segment in Leads II, III, and Lead V_F, and in a number of the unipolar precordial leads. It was probably caused by almost continuous acute myocardial injury as the neoplastic tissue infiltrated the cardiac musculature.

The authors wish to acknowledge their appreciation of the valuable suggestions and assistance of Dr. Frank N. Wilson in this study.

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HEART BLOCK

The Influence of Ventricular Systole Upon the Auricular Rhythm in Complete and Incomplete Heart Block

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THEORETICALLY, when heart block is complete, electrical communication between auricles and ventricles is severed. The two sets of heart chambers then beat in response to their own independent pacemakers, and with their own rate and rhythm. In many cases of auriculoventricular block, however, the contractions of the ventricles appear to disturb the auricular rhythm, with the result that the intervals between auricular contractions during which ventricular systole occurs are shorter than those during which the ventricles are inactive (Fig. 1).

This curious arrhythmia was first described by Erlanger and Blackman[1] in a study of experimental heart block. They observed that each ventricular systole produced a marked slowing of the auricular rate. In some instances this slowing was so great that only one auricular beat occurred between two consecutive ventricular beats. When several auricular beats occurred between ventricular beats, the first interauricular interval was long, and the following auricular periods became gradually shorter. To explain these observations they adopted the view that vagal tone is increased with each arterial pulse. Hecht[2] first noted this arrhythmia clinically, in a child suffering from the Morgagni-Adams-Stokes syndrome. Wilson and Robinson[3] reported two cases in more detail. They discovered a tendency for the auricular arrhythmia to disappear when the heart rate was rapid as a result of exercise or the administration of atropine, thus lending support to the view that it was dependent upon vagus activity. In their second case (as well as in the one described by Cohn and Fraser[4]), the auricular complexes which followed the beginning of ventricular systole were aberrant. They assumed that an ectopic auricular focus, stimulated mechanically by the contracting ventricle, had given rise to these aberrant complexes. They further ventured the suggestion that a similar effect of ventricular systole upon the ordinary auricular pacemaker might account for the arrhythmia described above. Wenckebach and Winterberg[5] offered still another explanation. They believed that the auricular irregularity was caused by changes in the blood supply of the sinus pacemaker consequent upon ventricular systole. In a clinical study of 43 cases of complete heart block, Ellis[6] noted the auricular arrhythmia in six of them, and several other authors have mentioned the fact that this phenomenon

Received for publication June 3, 1943.
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does occur.[7,8,9,10] Lewis[7] observed that the irregularity is often more striking in degree in 2:1 auriculoventricular block.

We were unable to find in the literature a detailed study of a large series of cases of heart block which was devoted primarily to an analysis of this problem. We thought, therefore, that the following review of 28 cases of complete, and 10 cases of incomplete, heart block, analyzed from this particular standpoint, might throw some light on the true nature of this mechanism.

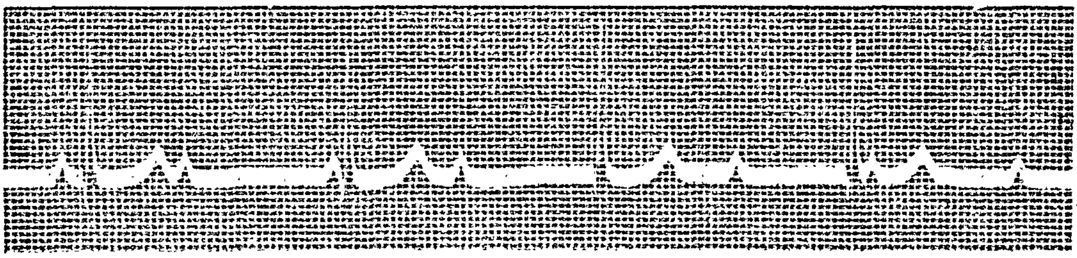

Fig. 1.—Case 28, Lead III.

As-Vs-As cycles shorter. P_1P_2 - 70; P_1R_1 - 17; R_1P_2 - 53; P_2P_3 - 85; P_3P_4 - 73; P_3R_2 - 8; R_2P_4 - 65; (P_4P_5 - ?, P_5P_6 - ?; = 157); P_6P_7 - 78; P_6R_4 - 68; R_4P_7 - 10; P_7P_8 - 83.

MATERIAL

The cases were obtained from the files of the Newark Beth Israel Hospital and from our own private practice. Many were discarded because the auricular complexes were not sharply enough defined to allow accurate measurement, or because of the presence of auricular fibrillation, auricular flutter, or frequent premature ventricular contractions. All of the intervals between auricular complexes were carefully measured, as were the interventricular intervals. Estimation to the nearest $\frac{1}{100}$ second was considered sufficiently accurate for our purpose. The lengths of the auriculo-ventriculo-auricular cycles were compared with those of the auriculo-auricular cycles. For the sake of brevity, the former cycles will be designated As-Vs-As, and the latter, As-As, throughout this paper. In some instances the auriculoventricular and ventriculoauricular intervals were also measured.

In four cases repeated tracings had been taken. In two of these, the shortening of the As-Vs-As cycle did not occur on all occasions. Nevertheless, they were included in the group which illustrated this phenomenon, thus slightly weighting the statistics in its favor.

In all, 28 cases of complete block and 10 of incomplete block were studied. Two showed variations from complete to incomplete block, and were included in both series. Thus, there were 36 individual case histories. In the group of cases of incomplete heart block, there were 8 examples of 2:1 block, one of the Wenckebach phenomenon, and one of intermittent high-grade block.

Data as to age, sex, etiology, and auricular and ventricular rates, as well as the results of measurements, will be found in Table I.

RESULTS

Early in this study the necessity for careful measurement was demonstrated by the observation that, when a ventricular complex falls be-

tween two auricular complexes, an optical illusion results, and this cycle may appear shorter than the preceding or following As-As cycle, although actually it may be longer (Fig. 2). Also, slight changes in

TABLE I

CASE	E.G.	AGE	SEX	ETIOLOGY	INTERAURICULAR INTERVAL (0.01 SEC.)	INTERVENTRICULAR INTERVAL (0.01 SEC.)	As-Vs-As SHORTER	As-As SHORTER	NO CORRELATION	REMARKS
					Complete Block					
1	32	55	M	A.S.	73-78	226	x	-	-	
2	208	65	M	A.S.	78-80	216	-	-	x	
3	347	77	M	A.S.	64-71	202	-	-	x	
4	384	73	M	A.S.	64-66	151	-	-	x	
5	732	42	F	?	62-75	172	x	-	-	
6	893	65	M	A.S.	67-72	165	x	-	-	
7	935	75	M	A.S.	84-90	157	x	-	-	Auricular premature contractions
8	941	72	F	C.O.	51-62	152	-	x	-	Auricular tachycardia
9	1029	78	M	A.S.	70-76	196	x	-	-	
10	1037	68	F	A.S.	62-64	206	-	-	x	
11	1396	55	F	C.O.	68-72	186	-	-	x	
12	1961	61	M	A.S.	54-59	160	-	x	-	Auricular tachycardia
13	2238	72	M	A.S.	86-102	174	-	-	x	
14	2835	81	F	A.S.	46-74	148	x	-	-	Auricular premature contractions
15	2991	33	F	?	56-63	94	x	-	-	Auricular tachycardia
16	3439	57	M	A.S.	68-84	140	-	-	x	
17	3690	92	F	A.S.	56-62	134	x	-	-	Auricular tachycardia
18	4148	47	F	SYPH.	58-61	182	x	-	-	Auricular tachycardia
19	4379	70	M	C.O.	67-68	200	-	-	x	
20	4540	63	F	A.S.	78-84	166	x	-	-	
21	O-HG	68	M	A.S.	82-88	174	x	-	-	
22	4835	63	M	A.S.	120-152	190	-	-	x	Auricular bradycardia; phasic arrhythmia
23	4693	65	F	A.S.	80-88	182	-	-	x	
24	O-EB	65	M	A.S.	54-56	220	-	-	x	Auricular tachycardia
25	O-PC	62	M	A.S.	64-82	210	x	-	-	
26	MW-1	41	F	SYPH.	72-88	128	x	-	-	
27	O-AE	56	M	A.S.	72-81	217	-	-	x	
28	O-HS	9	M	CONG.	65-85	130	x	-	-	

TABLE I—CONT'D

CASE	ECG	AGE	SEX	ETIOLOGY	INTERAURICULAR INTERVAL (0.01 SEC.)	INTERVENTRICULAR INTERVAL (0.01 SEC.)	As-Vs-As SHORTER	As-As SHORTER	NO CORRELATION	REMARKS
					Incomplete Block					
1	30				79-86	160	x	-	-	2:1 block
26	MW-2				68-72	84-128	x	-	-	High-grade intermittent block
29	93	42	F	DIG.	53-54	104	-	-	x	2:1 block; auricular tachycardia
30	1526	68	M	A.S.	74-80	154	-	x	-	2:1 block
31	2511	65	F	A.S.	74-84	156	-	x	-	2:1 block
32	2935	50	M	C.O.	72-76	142	x	-	-	Wenckebach phenomenon
33	3196	62	M	INF.	50-54	105	-	-	x	2:1 block; auricular tachycardia
34	3854	58	M	A.S.	96-104	200	x	-	-	2:1 block; auricular bradycardia
35	6239	72	M	A.S.	75-82	160	-	-	x	2:1 block
36	4398	66	M	C.O.	56-60	116	x	-	-	2:1 block; auricular tachycardia

Abbreviations: A.S.—Arteriosclerosis; ?—unknown; C.O.—coronary occlusion; SYPH.—syphilis; CONG.—congenital; DIG.—digitalis; INF.—acute infection.

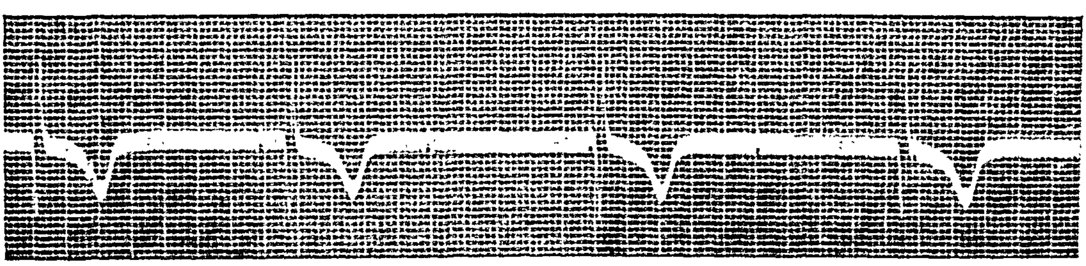

Fig. 2.—Case 13, Lead IV.
Note optical illusion. P_3P_4 appears longer, but is actually shorter than P_2P_3 and P_4P_5. P_1P_2 - 103; P_2P_3 - 100; P_3P_4 - 98; P_4P_5 - 104; P_5P_6 - 97.

camera speed may give a false impression as to time intervals on cursory inspection of a record.

The As-Vs-As cycles were shorter than the As-As cycles in 14 (50 per cent) of the cases of complete block (Fig. 1). In 2 instances (7.1 per cent) the As-As cycles were shorter (Fig. 3), and, in 12 (42.9 per cent), there was no definite correlation between the lengths of the two types of cycles. In the latter event, either the sinus rhythm was perfectly regular (Fig. 4), or the relationship between As-Vs-As and As-As cycle lengths varied (Fig. 5).

Of the series of cases of incomplete heart block, in five instances (50 per cent) the As-Vs-As cycles were shorter (Fig. 6), in 2 (20 per cent), the As-As cycles were shorter (Fig. 7), and in 3 (30 per cent) there was no correlation (Fig. 8).

Among the 14 cases of complete block in which the As-Vs-As cycles were shorter, there were 10 instances of normal auricular rate (i.e., 60 to 100 per minute), in 2 of which the rhythm was interrupted by auricular

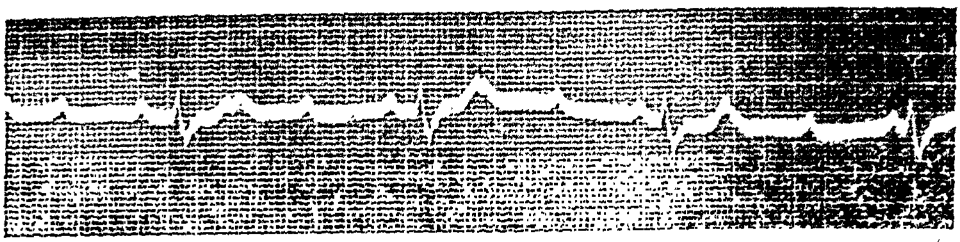

Fig. 3.—Case 12, Lead II.
As-As cycles shorter, rapid auricular rate. First As-As cycles longer than second. P_1P_2 - 54; P_2P_3 - 59; P_3P_4 - 51; P_4P_5 - 56; P_5P_6 - 58; P_6P_7 - 51; P_7P_8 - 54; P_8P_9 - 60; P_9P_{10} - 54; $P_{10}P_{11}$ - 56.

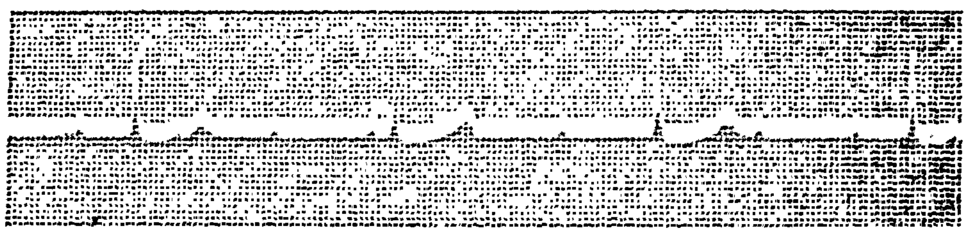

Fig. 4.—Case 11, Lead I.
Auricular rhythm constant. P_1P_2 - 68; P_2P_3 - 68; P_3P_4 - 68; P_4P_5 - 68; P_5P_6 - 68; P_6P_7 - 68; P_7P_8 - 68; P_8P_9 - 68.

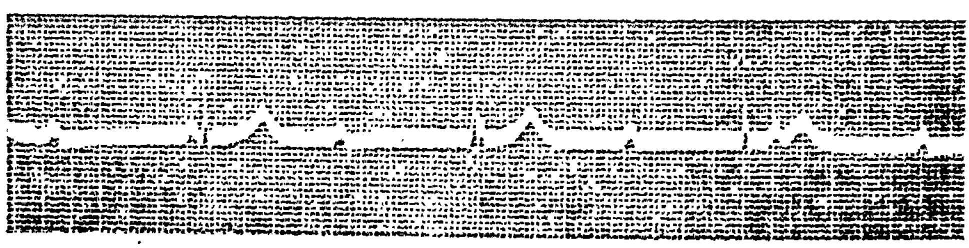

Fig. 5.—Case 13, Lead II.
No correlation between As-Vs-As and As-As cycle lengths. P_1P_2 - 96; P_2P_3 - 100; P_3P_4 - 98; P_4P_5 - 102; P_5P_6 - 98; P_6P_7 - 100.

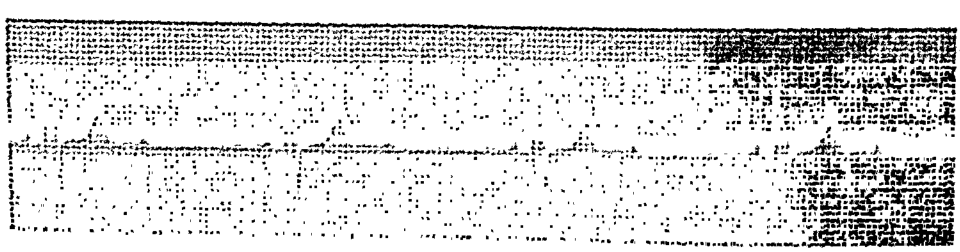

Fig. 6.—Case 1, Lead I.
2:1 auriculoventricular block. As-Vs-As cycles shorter. P_1P_2 - 82; P_2P_3 - 84; P_3P_4 - 82; P_4P_5 - 86; P_5P_6 - 82; P_6P_7 - 84; P_7P_8 - 82.

premature contractions (Fig. 9), 3 instances of tachycardia (Fig. 12), and 1 of bradycardia with marked phasic arrhythmia (Fig. 11). Of the 6 cases of complete block in which the auricular rate exceeded 100 per minute, the As-Vs-As cycles were shorter in 3 (Fig. 12), longer in 2 (Fig. 3), and in 1 there was no correlation (Fig. 10). Thus, the observation of Wilson and Robinson[3] that there is a tendency for the shortening of the As-Vs-As cycles to disappear in the presence of tachycardia is not confirmed. No relationship was detected between the

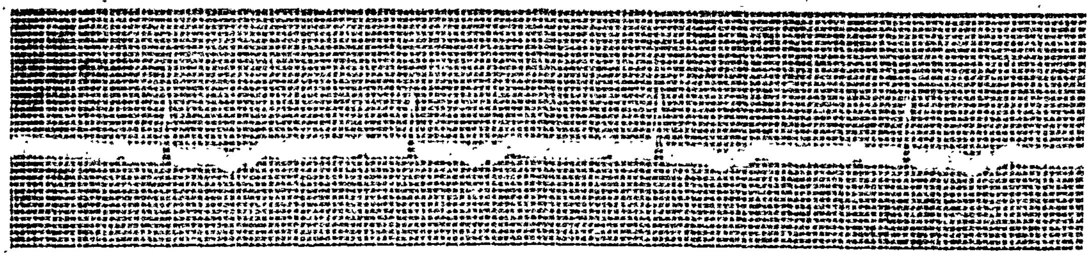

Fig. 7.—Case 30, Lead I.
2:1 auriculoventricular block. As-As cycles shorter. P_1P_2 - 78; P_2P_3 - 74; P_3P_4 - 78; P_4P_5 - 74; P_5P_6 - 78; P_6P_7 - 77; P_7P_8 - 78.

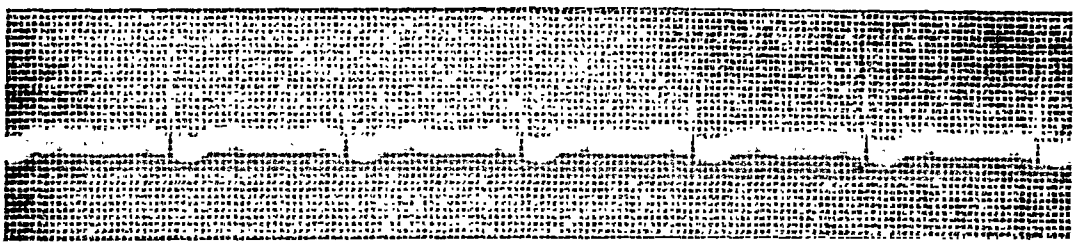

Fig. 8.—Case 29, Lead I.
No correlation between As-Vs-As and As-As cycle lengths. P_1P_2 - 54; P_2P_3 - 54; P_3P_4 - 54; P_4P_5 - 53; P_5P_6 - 54; P_6P_7 - 54; P_7P_8 - 52; P_8P_9 - 54; P_9P_{10} - 53; $P_{10}P_{11}$ - 53; $P_{11}P_{12}$ - 53.

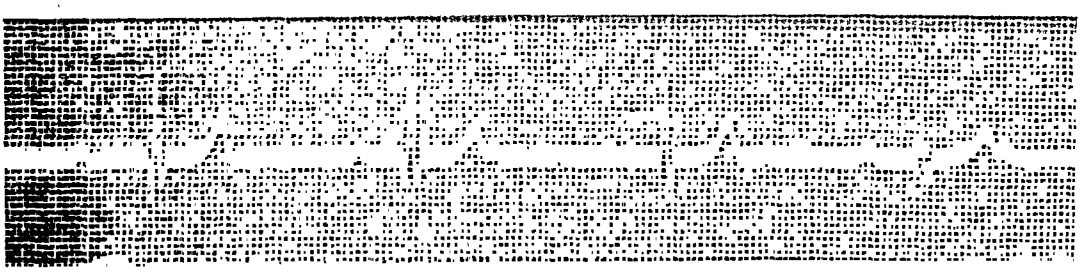

Fig. 9.—Case 7, Lead II.
Auricular premature contraction. P_1P_2 - 84; P_2P_3 - 86; P_3P_4 - 84; P_4P_5 - 42; P_5P_6 - 105; P_6P_7 - 87; P_7P_8 - 84.

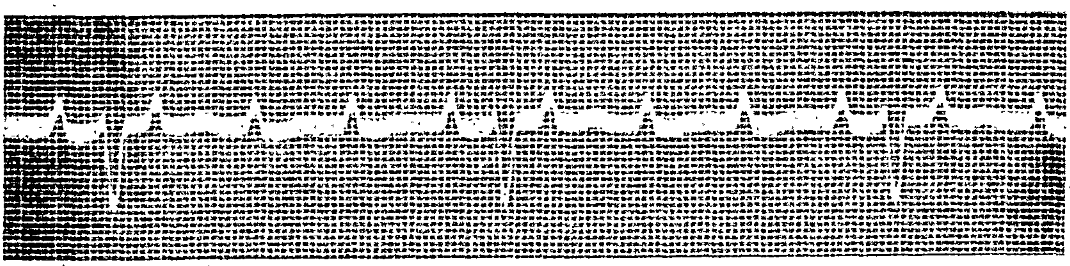

Fig. 10.—Case 24, Lead II.
Rapid auricular rate, no correlation between As-Vs-As and As-As cycle lengths. P_1P_2 - 56; P_2P_3 - 56; P_3P_4 - 56; P_4P_5 - 56; P_5P_6 - 56; P_6P_7 - 56; P_7P_8 - 56; P_8P_9 - 56; P_9P_{10} - 56; $P_{10}P_{11}$ - 56.

occurrence of shortening of the As-Vs-As cycles and the ventricular rate.

Among the cases of incomplete block, there were 3 instances of tachycardia, 1 of bradycardia, and 6 of normal auricular rate.

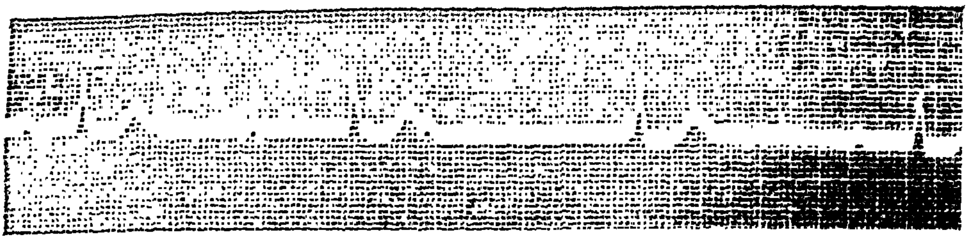

Fig. 11.—Case 22, Lead II.
Slow auricular rate with marked phasic arrhythmia. P_1P_2 - 160; P_2P_3 - 118; P_3P_4 - 140? P_4P_5 - 151?

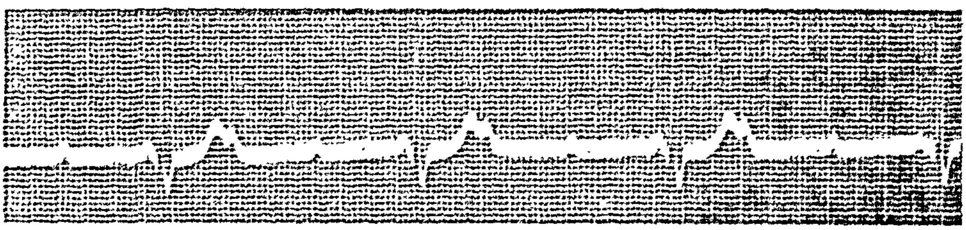

Fig. 12.—Case 18, Lead I.
Rapid auricular rate, As-Vs-As cycles shorter. P_1P_2 - 59; P_2P_3 - 59; P_3P_4 61; P_4P_5 - 61; P_5P_6 - 59; P_6P_7 - 60; P_7P_8 - 59; P_8P_9 - 58; P_9P_{10} - 61; $P_{10}P_{11}$ - 61.

COMMENT

Since in 42.9 per cent of our series of cases of complete block there was no definite correlation between the lengths of the As-Vs-As and As-As intervals, it might appear that the occurrence of shortening As-Vs-As cycles is simply fortuitous, and that ventricular systoles fall by chance alone within the shorter interauricular cycles during sinus arrhythmia, particularly when the ventricular rate is slow and approximates the respiratory rate. However, reference to Table I would indicate that the wide variation in ventricular rates in the cases in which there were shorter As-Vs-As cycles discounts this possibility, for in most cases the ventricular rate far exceeds the physiologic respiratory rate, as well as the time intervals between changing rates in nonphasic sinus arrhythmia. Furthermore, we should expect the ventricular systoles to fall during the longer interauricular periods with equal frequency. Actually, the latter occurred in but 7.1 per cent of the cases of complete block, and in 20 per cent of the shorter series of incomplete block. Moreover, the shortening of As-Vs-As cycles was usually consistent throughout all leads and throughout the long tracings which were taken on several of the patients.

Three theories have been advanced in an attempt to explain the apparent influence of ventricular systole upon the auricular rhythm in

auriculoventricular block. These are as follows: (1) changes in the blood supply to the sinus node; (2) changes in vagal tone; and (3) direct stimulation of the sinoauricular pacemaker by the contracting ventricle.

Changes in the Blood Supply to the Sinus Node.—This theory was first propounded by Wenckebach and Winterberg.[5] After contraction of the left ventricle, the sinoauricular pacemaker receives a fresh supply of oxygenated blood, its nutrition is improved, waste products of its metabolism are removed, and, consequently, impulse formation is stimulated. During periods of ventricular asystole the reverse process holds true, and the pacemaker is depressed.

In order to put this theory to the test, several cases were analyzed with respect to the time in the As-Vs-As cycle during which ventricular systole occurred. If this hypothesis be correct, we might rightfully anticipate an optimum point in the cycle at which stimulation of the pacemaker should take place, with a resultant As-Vs-As cycle shorter than any other in the record. However, actual analysis failed to disclose any such correlation of the As-Vs-As cycle length with the point of incidence of Vs in the cycle (Table II). Furthermore, even when the Vs was found very late in the cycle, shortening was present, although the second As appeared during the isometric contraction phase of the preceding ventricular systole (Fig. 1; note cycle P_6-QRS-P_7).

TABLE II

AS-VS-AS CYCLE INTERVAL	P-P INTERVAL	P-R INTERVAL	R-P INTERVAL
P_4P_5	78	32	46
P_7P_8	82	38	44
$P_{10}P_{11}$	79	38	41
$P_{12}P_{13}$	81	2	79
$P_{14}P_{15}$	82	74	8
$P_{16}P_{17}$	80	34	46
$P_{19}P_{20}$	78	19	59
$P_{20}P_{21}$	84	72	12
$P_{22}P_{23}$	76	26	50

Case 26. ECG MW-1. Note length of P-P interval independent of point of incidence of ventricular systole.

Changes in Vagal Tone.—Erlanger and Blackman[1] contended that vagal tone is enhanced by each arterial pulse. Because of this increased nervous activity, the As-As cycles which follow ventricular contractions are lengthened. Should we accept this theory, we might anticipate that, when two or more As-As cycles follow a ventricular contraction, the first would be longer than subsequent ones. There were 14 cases in which two or more As-As cycles were present between ventricular contractions. In 7 of these the first As-As cycles were longest (Fig. 3), in 2 the second was longest (Fig. 13), and in 5 there was no correlation (Fig. 14). From the above it can readily be seen that, although the concept is borne out to a greater or lesser degree, there are definite excep-

tions that must be reckoned with. Moreover, there is no relationship between the point of incidence of Vs in the As-Vs-As cycle and the length of the first As-As cycle which follows.

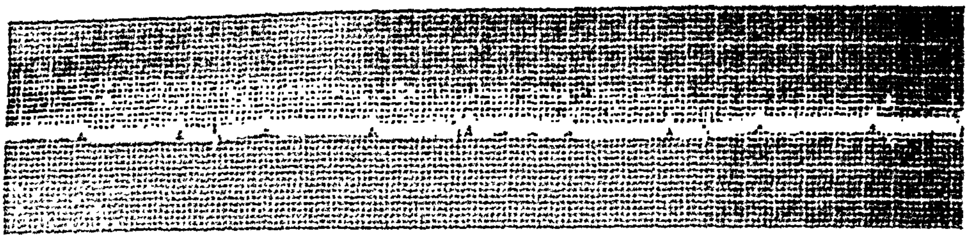

Fig. 13.—Case 5, Lead III.
First As-As cycle largest. P_1P_2 - 69; P_2P_3 - 60; P_3P_4 - 74; P_4P_5 - 66; P_5P_6 - 66; P_6P_7 - 68; P_7P_8 - 61; P_8P_9 - 76.

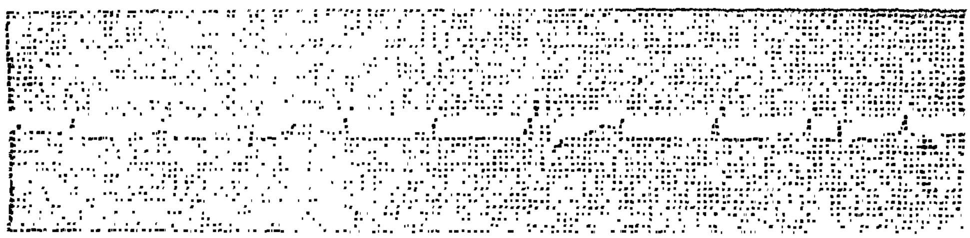

Fig. 14.—Case 10, Lead II.
No correlation between lengths of first and second As-As cycles following As-Vs-As cycles. P_1P_2 - 62; P_2P_3 - 62; P_3P_4 - 62; P_4P_5 - 62; P_5P_6 - 62; P_6P_7 - 62; P_7P_8 - 62; P_8P_9 - 62; P_9P_{10} - 62.

Direct Stimulation of the Sinoauricular Pacemaker by the Contracting Ventricle.—Rare instances have been recorded of complete heart block in which the ventricular contractions appeared to initiate ectopic auricular impulses which were not the result of retrograde conduction. The explanation advanced for this phenomenon is that the contraction of the ventricle mechanically stimulates an irritable ectopic auricular focus. Based on this reasoning, the further inference is made that ventricular systole might similarly stimulate the normal sinus pacemaker, and induce it to discharge prematurely. The validity of this theory is challenged by Wolferth and McMillan.[11] After a very exhaustive analysis of relatively short intervals between ventriculoauricular sequential beats during high grade heart block, they conclude that this phenomenon is caused by retrograde transmission of the excitatory process through the area of block; it cannot be satisfactorily explained as the result of mechanical stimulation of auricles by ventricles. In two of our cases of complete heart block, sporadic premature auricular contractions were present (Fig. 9). We did not encounter any instances of ectopic auricular complexes like those described by Wilson and Robinson[2] or Cohn and Fraser,[4] nor ventriculoauricular sequential beats of the type reported by Wolferth and McMillan.[11] In several graphs, minor changes in the contour of P waves which followed QRS complexes were noted, but were regarded in all likelihood as the result of a shift in the electrical axis of the auricles caused by contraction of the ventricles.

Each of the foregoing hypotheses may embody factors which are in part responsible for the auricular irregularity. However, all of them are defective in two major respects. First, they fail to account for the fact that the lengths of the As-Vs-As cycles, or the succeeding As-As cycle, appear to be independent of the point of incidence of Vs in the As-Vs-as cycle. Second, they fail to explain away satisfactorily the exceptions to the rule, i.e., the cases in which As-As is shorter than As-Vs-As, and those in which there is no correlation at all.

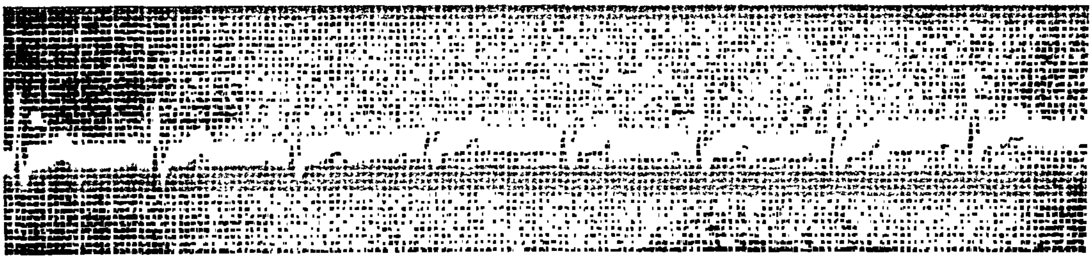

Fig. 15*A*.—Case 1, Lead II.
Normal sinus rhythm. P_1P_2 - 82; P_2P_3 - 82; P_3P_4 - 82; P_4P_5 - 82; P_5P_6 - 82; P_6P_7 - 82; P_7P_8 - 82.

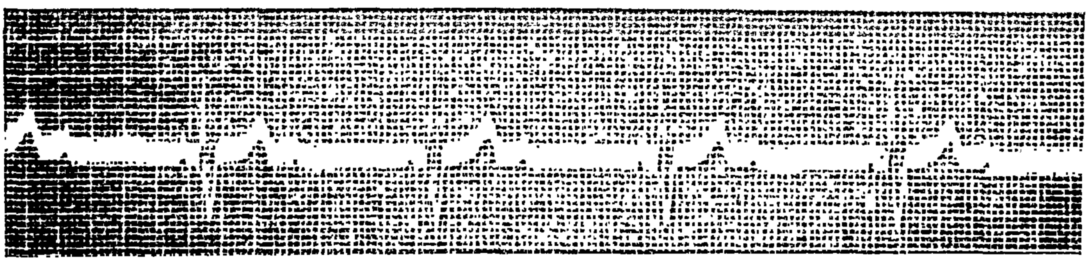

Fig. 15*B*.—Case 1, Lead I.
2:1 auriculoventricular block. P_1P_2 - 72; P_2P_3 - 69; P_3P_4 - 71; P_4P_5 - 69; P_5P_6 - 72, P_6P_7 - 69; P_7P_8 - 72; P_8P_9 - 70.

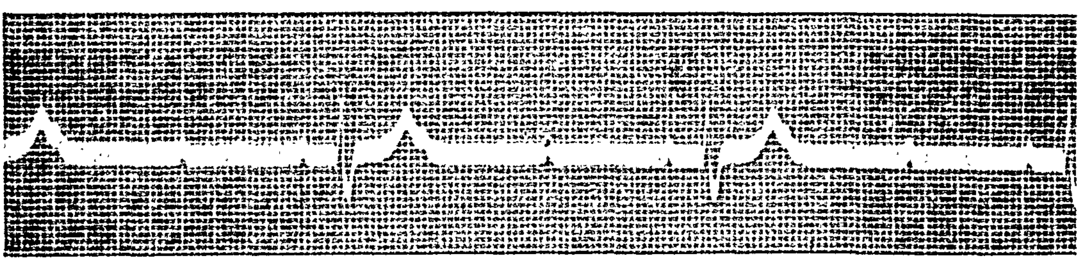

Fig. 15*C*.—Case 1, Lead I.
Complete auriculoventricular block. P_1P_2 - 78; P_2P_3 - 75; P_3P_4 - 74; P_4P_5 - 76; P_5P_6 - 74; P_6P_7 - 74; P_7P_8 - 76; P_8P_9 - 74.

When normal sinus rhythm is present, the ventricular systole does not appear to disturb the relationship of succeeding beats, for otherwise there would be progressive acceleration or retardation of the auricular rate. In this connection, it is interesting to note that interpolated ventricular premature beats do not appreciably alter a normal sinus mechanism.

Fig. 15 shows a series of tracings from a case of intermittent block of varying degree. The first one (Fig. 15*A*) shows normal sinus rhythm; the second (Fig. 15*B*), 2:1 auriculoventricular block, and the auricular

arrhythmia is quite marked, as it is also in the third tracing (Fig. 15C), in which the block is complete. Since in the first tracing the auricular rhythm is perfectly regular, the question may be asked: Why, when 2:1 block or complete block supervenes, is the auricular rhythm disturbed? The fact that we have been unable to detect any relationship between the point of incidence of ventricular systole in the As-Vs-As cycle and the duration of this cycle or succeeding As-As cycles impels us to the conclusion that it is the mere absence of ventricular activity in the As-As cycle which determines its lengthening. In the absence of a ventricular beat, it appears that the sinoauricular pacemaker hesitates, so to speak, before discharging. Is, then, the presence of ventricular systole in itself a prerequisite to the orderly, rhythmic discharge of the sinoauricular pacemaker? And is the stimulus mediated through humoral, nervous, or mechanical channels? Is it possible that mechanical stimulation depends upon the rise in intra-auricular tension which accompanies the isometric contraction phase of the right ventricle?

It is probable that the stimulus, or perhaps more correctly, the absence of the stimulus from the contracting ventricle upon the auricular pacemaker is of a low order of intensity. Furthermore, the sensitivity of individual pacemakers probably varies. Some normal persons have very labile heart rates, and respond readily to stimuli of various kinds, whereas others exhibit a much more stable cardiovascular mechanism. Depending upon the intensity of the stimulus and the sensitivity of the receptor, it is conceivable that the ventricular beats would influence the auricular rate in certain cases, but not in others. Still another factor may play a role in explaining the exceptional cases, i.e., those in which As-As is shorter or in which there is no correlation. During periods of ventricular asystole the auricles continue to contract independently, and tend to expel blood into the ventricles. Since the ventricles do not empty with equal frequency, between arterial pulses there is a rise in intra-auricular tension which is reflected in the large auricular waves in the jugular pulse, and in some cases by audible auricular sounds.[12] High voltage P waves have been regarded as evidence of auricular strain.[13] In this connection, it is interesting to note that in eight of our cases of complete heart block there were high voltage P waves in Lead II, and, in addition, in Lead III in two of these (Figs. 10 and 14). This increase in intra-auricular tension is, per se, a stimulus to acceleration of the auricular rate, i.e., the Bainbridge reflex. Thus, there would be operative, simultaneously, two opposing influences: one, dependent upon the absence of ventricular systole, tending to lengthen the As-As period, and the other, dependent upon the Bainbridge type of reflex, tending to shorten this period. If the first stimulus be dominant, the As-As cycles will be longer, whereas if the second stimulus be more intense, they would be shorter, and if the opposing influences be nearly equal, there would be no correlation.

CONCLUSIONS

1. The auricular arrhythmia which is present in some cases of complete and incomplete heart block appears to be caused primarily by the absence of ventricular systole from the interauricular periods. The mere failure of the ventricular beat disturbs the normal, orderly synchronization between auricular and ventricular activity, and results in delay in the discharge of the sinoauricular pacemaker.

2. The reflex mechanism which is involved is unknown. It may be of a humoral, nervous, or mechanical nature.

3. Because of variations in the intensity of the stimulus in the absence of ventricular systole from the As-As cycle, and in the sensitivity of the receptor in the sinoauricular node, the arrhythmia may or may not occur.

4. The rise in intra-auricular pressure during ventricular asystole tends reflexly to accelerate the auricular rate. This may explain the cases in which the As-As cycles are shorter, or those in which there is no correlation between As-Vs-As and As-As cycle lengths.

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CONGENITAL CARDIAC DISEASE
BIBLIOGRAPHY OF THE 1,000 CASES ANALYZED IN MAUDE ABBOTT'S ATLAS

WITH AN INDEX

EDITED BY DONALD DEF. BAUER, M.D., C.M., AND
EFFIE C. ASTBURY, B.A., B.L.S.

THE purpose of this bibliography is best expressed by a quotation from a letter of Dr. Lewis T. Bullock. He encountered difficulty in tracing the source of Dr. Abbott's material, and he therefore suggested the preparation of such a bibliography to Dr. Abbott during the last year of her life. His suggestion lived on in the mind of one of the editors, who at that time was associated with Dr. Abbott as student and assistant. Dr. Bullock has written:

"I still feel very strongly that the publication of this bibliography would be of great value. Dr. Abbott's statistics are very widely quoted and yet many people undoubtedly have found, as I did, that it was impossible to analyze these statistics because the source of them could not be determined, except by personal communication with Dr. Abbott. As you know, my statistics vary markedly from hers. This is because I excluded the infants, while she included a large number of infants. Such comparison is, however, impossible, and the discrepancy cannot be explained unless one is able to go back and check the material which she used. The value of her excellent chart will be tremendously increased by publication of a complete bibliography."

To obviate the difficulties which Dr. Bullock and others met in utilizing material from Dr. Abbott's chart, a reference is herewith provided for every one of the 1,000 cases which she analyzed.* These are arranged alphabetically under the subject headings of the chart. Whenever possible, the editors have included information about age and sex. This is given at the end of the *reference*: the number refers to years unless otherwise designated; "m" is for male, and "f" for female.

Dr. W. W. Francis, of the Osler Library, McGill University, very kindly made available the papers of Dr. Abbott on which were found brief notes about the 1,000 cases, including abbreviated references to the books or papers wherein the cases were originally described. The special library training of one of the editors, the generous cooperation of Dr. Archibald Malloch, Librarian for the New York Academy of Medicine, and Mr. Frankenberger, Librarian for the Kings County Medical Society, in making available the facilities of their fine libraries, the invaluable work of stack assistants at McGill and the other libraries, and the important clues provided by the *Surgeon General's Catalogue* and the *Index Medicus* enabled the editors to trace all but a small hand-

Received for publication June 8, 1942.

*In a few instances the date of a reference is later than the date of publication of the chart. This apparent inconsistency is explained by the fact that these items were recorded on the chart as personal communications, but from the data given it was possible to identify them in their subsequent published form.

ful of the incomplete references to the correct source. Alternate references found in Dr. Abbott's notes are provided for the remaining doubtful cases. It is a pleasure to acknowledge also the valuable help of Miss Hazel Watts, who contributed generously of her time early in the undertaking. The interest and the guidance of Dr. J. C. Meakins, Dr. Paul White, Dr. W. W. Francis, Dr. Archibald Malloch, Dr. Emanuel Libman, and others have made possible the completion of this undertaking.

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77. Pope, Charles. A case of transposition of the heart, Lancet 2: 9, 1882. 41 m.

III. ANOMALIES OF THE HEART AS A WHOLE

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81. Shattock, S. G. A heart with bifid apex, Tr. Path. Soc. Lond. 42: 67-71, 1891. 25.

2. Diverticulum—3 cases

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83. Koller-Aeby, H.: Ein angeborenes Herzdivertikel in einer Nabelschnurhernie, Arch. f. Gyn. 82: 185-187, 1907. 7 mo. fetus f.
84. Mahrburg, S.: Ueber einen Fall von angeborenem Divertikel des Herzens, Virchow's Arch. f. path. Anat. 277: 498-500, 1930. 3 days m.

3. Primary congenital hypertrophy—15 cases

85. Abbott, M. E. Congenital cardiac disease. In Modern medicine; ed. by William Osler and Thomas McCrae; 3rd ed. Phila., Lea & Febiger, 1927. v. 4, p. 612-812. Case p. 666, 3 mo. f.
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87. Carrington, G. L. & Krumbhaar, E. B. So-called idiopathic cardiac hypertrophy in infancy, Am. J. Dis. Child. 27: 449-455, 1924. 12 mo. f.
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97. Berger, Louis & Vallée, Arthur. Les rhabdomyomes congénitaux du coeur, Ann. d'anat. path. 7: 797-811, 1930. 2 m.

98. Farber, Sidney. Congenital rhabdomyoma of the heart, Am. J. Path. 7: 105-130, 1931. 6 mo. f.

99.*Hlava, Jaroslav. Rhabdomyom levého srdce, Sborník lékärský, 1886 or 1887. 14 days.

100. Knox, J. H. M. & Schorer, E. H. A multiple rhabdomyoma of the heart muscle, Arch. Pediat. 23: 561-567, 1906. 7 mo.

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103. Seiffert. Die congenitalen multiplen Rhabdomyome des Herzens, Beitr. z. path. Anat. u. z. allg. Path. 27: 145-172, 1900. 18 mo. m.

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105. Uehlinger, Erwin. Ueber einen Fall von diffusem Rhabdomyom des Herzens, Virchow's Arch. f. path. Anat. 258: 719-730, 1925. 20 m.

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5. *Congenital heart block—3 cases*

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IV. ANOMALOUS SEPTA OR CHORDAE

1. *Anomalous septa*

a) *In left auricle—10 cases*

111. Borst, M. Ein cor triatriatum, Verhandl. d. deutschen path. Gesellsch. 9: 178-192, 1905. 38 f.

112. Church, W. S. Congenital malformation of the heart; abnormal septum in left auricle, Tr. Path. Soc. Lond. 19: 188-190, 1868. 38 f.

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114. Griffith, T. W. Note on a second example of division of the cavity of the left auricle into two compartments by a fibrous band, J. Anat. & Physiol. 37: 255-257, 1902-03. 48 m.

115. Hosch, P. H. Zur Lehre des Missbildungen des linken Vorhofs: I Ein Sehnenfaden im linken Vorhof; II Ein Herz mit linken Doppelvorhof, Frankfurt. Ztschr. f. Path. 1: 563-580, 1907. Case 2, 25 f.

116. Palmer, G. A. Cardiac anomaly (so-called double left auricle); case, Am. Heart J. 6: 230-236, 1930-31. 3½ mo. m.

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b) *In right auricle—4 cases*

121. Möllendorf, W. Ueber abnorme Erhaltung der Sinusklappen im rechten Vorhof eines menschlichen Herzens, Anat. Anz. 40: 406-409, 1911-12.

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c) *In ventricles—3 cases*

125. Dudzus, Max. Ein Beitrag zur Lehre vom "dritten Ventrikel" im Anschluss an eine kombinierte Herzmissbildung mit drittem und akzessorischem Ventrikel, Virchow's Arch. f. path. Anat. 242: 24-34, 1923. 10 wk. m.

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129. Helwig, F. C. Personal communication. 58 f.

130. Hosch, P. H. *vide* 115. Case 1, 52 m.

131. Kleine, H. O. Zur Morphologie der Missbildungen des linken Vorhofs. (Chorda tendinea spuria atrii sinistri), Virchow's Arch. f. path. Anat. 267: 281-289, 1928. 84 f.

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133. de Vecchi, Bindo. Una rara forma di corda tendinea aberrante, Anat. Anz. 20: 374-380, 1901. 64.

b) *In right auricle—5 cases*

134. Chiari, H. Ueber Netzbildungen im rechten Vorhofe des Herzens, Beitr. z. path. Anat. u. z. allg. Path. 22: 1-10, 1897. Case 1, 24 m.

135. Yater, W. M. Variations and anomalies of the venous valves of the right atrium of the human heart, Arch. Path. 7: 418-441, 1929. Case 4, 65 f.; case 5, 33 m.; case 7, 69 m.; case 11, 40 m.

c) *In ventricles—6 cases*

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142. Archer, R. S. Note on a congenital band stretching across the origin of the aorta, Dublin Quart. J. Med. Sci. 55: 405-406, 1878. 39 m.
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146. Weinstein, Seymour. An anomalous band across the channel of the aorta at the level of the aortic leaflets, Tr. Chicago Path. Soc. 12: 277-279, 1927. 50 m.

V. DEFECTS OF INTERAURICULAR SEPTUM

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148. Amberg, Samuel & Willius, F. A. Auricular flutter with congenital heart disease, Am. J. Dis. Child. 32: 99-104, 1926. 5 f.
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154. Cramer, A. & Frommel, E. Contribution à l'étude du rétrécissement mitral congénital associé à l'insuffisance interauriculaire, Arch. d. mal du coeur 16: 561-569, 1923. 41 f.
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2. Defects auricular septum above—10 cases

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3. Defects auricular septum below—18 cases

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192. Beriel. *vide* 151. Case 5, 33 m.
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197. Moore, Norman. Malformation of the heart, Tr. Path. Soc. Lond. 32: 39-41, 1881. 17 f.
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203. Söldner, Felix. Missbildungen der Vorhofscheidewand des Herzens, Ostium primum persistens, Munich thesis, 1904. 84 pp. 30 m.
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205. Tylecote, F. E. *vide* 177. Case 2, 39 f.
206. Zeidler, Hugo. *vide* 179. Case 3, 8 mo. f.

4. *Multiple defects, auricular septum—5 cases*

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211. Welch, J. E. Patent foramen ovale, Proc. New York Path. Soc. 3: 181-185, 1903. 16 m.

5. *Premature closure foramen ovale—3 cases*

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213. Osler, William. Cases of cardiac abnormalities, Montreal General Hosp. Rep. 1: 177-192, 1880. Case 1, 8 mo. fetus m.
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VI. DEFECTS OF INTERVENTRICULAR SEPTUM

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218. Cabot, R. C. Case records of the Massachusetts General Hospital no. 15451, New England J. Med. 201: 945-948, 1929. 4½ f.
219. Callender, G. W. Perforation of the septum ventriculorum; clots in some of the pulmonary arteries, undergoing various changes, Tr. Path. Soc. Lond. 9: 91-95, 1858. Adult m.
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224. Crawford, B. L. & Weiss, E. *vide* 88. Case 1, 49 f.
225. Dupré, Ernest. Communication congénitale des deux coeurs, par inocculsion du septum interventriculaire, Bull. Soc. anat. de Paris 66: 404-409, 1891. 4½ m. [Appears twice on chart.]
226. Falconer, F. M. A case of perforate inter-ventricular septum differentiated from pulmonary stenosis, Med. & Surg. Yrbk. Hosp. of Plattsburg 1: 127-130, 1929. 14 f.
227. Gordon, William. Perforate septum ventriculorum with infective endocarditis of the pulmonary valves, Brit. Med. J. 2: 1174-1177, 1897. 5 m.
228. Gutzeit, Kurt. Ein Beitrag zur Frage der [illegible] n Hand eines Falles von kongenitaler Defektbildung i [illegible] elseptum und von gleichzeitigem Defekt in dem diesem Septumdefekt anliegenden Klappenzipfel der Valvula tricuspidalis, Virchow's Arch. f. path. Anat. 237: 355-372, 1922. 26 f.
229. Hadden, W. B. A case of congenital cardiac disease, Tr. Path. Soc. Lond. 33: 50-52, 1882. 4 mo. f.
230. Hare, C. J. Aperture in the septum ventriculorum, partly closed by one curtain of the tricuspid valve, Tr. Path. Soc. Lond. 1: 207-208, 1848. 5 mo. f.
231. — —. Aperture in the septum ventriculorum, with malformation of the aortic valves, and imperfect closure of the foramen ovale, Tr. Path. Soc. Lond. 1: 208-210, 1848. 14 mo. m.
232. Hart, Carl. Ueber die Defekt im oberen Teile der Kammerscheidewand des Herzens mit Berücksichtigung der Perforation des häutigen Septums, Virchow's Arch. f. path. Anat. 181: 51-100, 1905. Case 6, 19 m.
233. Hebb, R. G. Defect of cardiac septum (interventricular); congenital heart disease, Tr. Path. Soc. Lond. 41: 57-58, 1890. 5 mo. f.
234. — —. Heart with congenital defects and inflammatory disease, Tr. Path. Soc. Lond. 48: 41-42, 1897. 18 f.
235. Hillier, Thomas. Congenital malformation of the heart; perforation of the septum ventriculorum, establishing a communication between the left ventricle and the right auricle, Tr. Path. Soc. Lond. 10: 110-111, 1859. 2⅓ f.
236. — —. Communication between the ventricles of the heart; tubercular peritonitis and ulceration of bowels, Tr. Path. Soc. Lond. 12: 76-77, 1861. 14 mo. m.
237. Horder, T. J. Infective endocarditis, Quart. J. Med. 2: 289-324, 1908-09. Case 1, 31 m.; case 3, 7 m.
238. Jenner, William. Heart exhibiting an aperture through the septum of the ventricles, Tr. Path. Soc. Lond. 2: 37, 1850. 18 m.
239. Kelly, Charles. Malformed heart; defective septum ventriculorum, Tr. Path. Soc. Lond. 22: 95, 1871. 6 f.
240. Laubry, Charles & Pezzi, C. Traité des maladies congénitales du coeur, Paris, Baillière, 1921. xv, 335 pp. Case p. 130-131, 19 m.
241. McGill Museum. 42 m.
242. McIntosh, C. A. Chronic endocarditis associated with defects of septum ventriculorum, Ann. Clin. Med. 4: 748-754, 1925-26. 44 f.

243. Mackenzie, H. W. G. Congenital disease of the heart with right-sided endocarditis, Tr. Path. Soc. Lond. 41: 58-59, 1890. 21 m.
244. Money, Angel. Aneurysm of heart; cerebral tumour; idiocy, Tr. Path. Soc. Lond. 38: 97-99, 1887. 5 f.
245. Morestin, H. Anomalies multiples chez un foetus à terme, Bull. Soc. anat. de Paris 72: 857-858, 1897. fetus f.
246. Moschcowitz, Eli. Vegetative endocarditis of the pulmonary valve; thrombosis of one of the branches of the right pulmonary artery; embolus of the left pulmonary artery; patent ventricular septum, Proc. New York Path. Soc. 14: 18-21, 1914. 29 f.
247. Müller, Hermann. Zur Klinik und pathologischen Anatomie des unkomplizierten offenen Septum ventriculorum, Deutsches Arch. f. klin. Med. 133: 316-331, 1920. Case 1, 6 mo. m.; case 2, 11 mo. f.; case 3, 6 mo. f.; case 5, 18 f.; case 6, 39 f.; case 7, 18 f.; case 8, 8 f.; case 9, 35 m.
248. Pritchard, Eric. A specimen of congenital malformation of the heart, Rep. Soc. Study Dis. Child. 4: 93, 1904. 4 mo. m.
249. Rolleston, H. D. Communication between the ventricles of the heart, congenital, Tr. Path. Soc. Lond. 42: 65-67, 1891. 11 m.
250. Tate, W. W. H. Case of malformation of the heart, Tr. Path. Soc. Lond. 43: 36, 1892. 22 m.
251. Thomson, John. On two cases of valvular heart disease, resulting from foetal endocarditis, Edinburgh Hosp. Rep. 2: 292-297, 1894. Case 1, 20 mo. m.
252. Tirard, Nestor. Malformation of the heart, Tr. Path. Soc. Lond. 32: 41, 1881. 5 mo. f.
253. Tuckwell & Harris. A case of ulcerative endocarditis in a child, affecting the pulmonary valves, with certain congenital defects in the heart, Lancet 1: 516-518, 1885. 4 m.
254. Weinstein, Seymour. Congenital perforate interventricular septum of heart accompanied by shortened median tricuspid leaflet and dilated pulmonary artery with two cusps, Tr. Chicago Path. Soc. 12: 279-282, 1927. 6 mo.
255. Whitley, G. Disease of the pulmonary artery and its valves, Guy's Hosp. Rep. 3: 252-260, 1857. Case 2, 36 f.

2. *Defects elsewhere or multiple—5 cases*

256. Bennetz, Ernst. Ueber zwei Fälle von angeborenem Herzfehler mit Septumdefect, Freiburg thesis, 1895. 37 pp. Case 2, 4 mo. f.
257. Duckworth, Dyce. Notes of a case in which there was a small aperture in the septum ventriculorum near the apex of the heart, J. Anat. & Physiol. 11: 183, 1876-77. Stillborn m.
258. Müller, Hermann. *vide* 247. Case 4, 1¾ m.
259. Weiss, Edward. Congenital ventricular septal defect in a man aged seventy-nine, Arch. Int. Med. 39: 705-709, 1927. 79 m.
260. Wilbouschewitch. Communication des ventricules du coeur sans cyanose. Dilatation des artères pulmonaires. Endartérite pulmonaire, Bull. Soc. anat. de Paris 66: 50-53, 1891. 25 f.

3. *Aneurysms of pars membranacea—7 cases*

261. Brooks, Harlow. Malformation of the heart. Proc. New York Path. Soc. 71-72, 1897-98. 39 f.
262. Cannell, D. E. Congenital aneurysm of the interventricular septum, Am. J. Path. 6: 477-484, 1930. Case 1, 24 m.; case 2, 60 m.
263. Curtin, R. G. A case of interventricular aneurysm opening into the right ventricle by ulcerative process, and aneurysm of the abdominal aorta, with autopsy, Philadelphia Hosp. Rep. 5: 37-38, 1902. 53 m.
264. Hare, C. J. Malformation of the septum ventriculorum from a patient who died of diphtheria, Tr. Path. Soc. Lond. 16: 80-81, 1865. 24 m.
265. Irvine, J. P. Defective muscular development of the cardiac ventricular septum; consequent septal aneurysm; displacement of an aortic valve by this aneurysm, Tr. Path. Soc. Lond. 29: 47-49, 1878. 50 m.
266. McGill Museum. 41 m.

VII. COMPLETE DEFECTS OF CARDIAC SEPTA

1. *Cor triloculare biventriculare—5 cases*

267. Gunn, F. D. & Dieckmann, J. M. Malformations of the heart including two cases with common atrio-ventricular canal and septum defects, and one with defect of the atrial septum (cor triloculare biventriculosum), Am. J. Path. 3: 595-616, 1927. Case 3, 2 mo. m.

268. Probyn-Williams, R. J. Unusual malformation of the heart, J. Anat. & Physiol. 28: 305-308, 1893-94, *also* Tr. Obst. Soc. Lond. 36: 3-4, 1895, *also* Am. Gyn. & Obst. J. 5: 400, 1894. 1 mo.
269. Ratner, Bret, Abbott, M. E. & Beattie, W. W. Rare cardiac anomaly; cor *triloculare biventriculare in mirror-picture dextrocardia with persistent* omphalo-mesenteric bay, right aortic arch and pulmonary artery forming descending aorta, Am. J. Dis. Child. 22: 508-515, 1921. 17 days f.
270. Wohl, M. G. Unusual case of congenital cardiac defect (cor triloculare) associated with transposition of pulmonary artery and arch of aorta, J. Lab. & Clin. Med. 10: 812-816, 1925. 7 mo. f.
271. Zadoc-Kahn, L. & Cousin, J. Sur un cas de malformation cardiaque congénitale; absence de cloison interauriculaire; diverticule borgne de la cloison interventriculaire, Bull. et mém. Soc. méd. d. hôp. de Paris, 49: 1446-1449, 1925. 31 m.

2. *Cor triloculare biatriatum—13 cases*

272. Ball, R. P. Cor biatria triloculare with transposition of arteries; case report with necropsy findings, Am. J. Dis. Child. 32: 84-88, 1926. 2½ m.
273. Clarke, Ernest. Malformation of heart, Tr. Path. Soc. Lond. 36: 178, 1885. 10 wk.
274. Hale, R. J. Case of a heart with a single ventricle, with observations on the production of cyanosis, Tr. Path. Soc. Lond. 4: 87-94, 1853. 19 wk. m.
275. Holmes, A. F. Case of malformation of the heart, Tr. Med.-Chir. Soc. Edinburgh 1: 252-259, 1824, *also* Montreal Med. J. 30: 522-533, 1901 [republished by Abbott]. 23 m.
276. McCrea, E. F. W. A case of cor triloculare biatria, Lancet 1: 1077, 1927. 10 wk. f.
277. Mann, J. D. Cor triloculare biatriatum, Brit. Med. J. 1: 614-616, 1907. 35 m.
278. Marchand, F. Eine seltene Missbildung des Herzens eines Erwachsenen (Transposition der grossen Arterien bei rudimentärem rechten Ventrikel), Verhandl. d. deutschen path. Gesellsch. 12: 174-187, 1908. 21 m.
279. Mills, E. S. Cor triloculare biatriatum with coarctation of the aorta and anomaly of the coronary arteries, J. Med. Research 44: 257-262, 1923-24. Infant.
280. Peacock, T. B. Case of malformation of the heart, both auricles opening into the left ventricle, and transposition of the aorta and pulmonary artery, Tr. Path. Soc. Lond. 6: 117-119, 1855. 8 mo. m.
281. Robertson, J. I. Congenital abnormality of the heart; a case of cor triloculare biatriatum, Lancet 1: 872-875, 1911. 9 wk.
282. Saenger, Alfred. Ueber einen Fall von Endocarditis ulcerosa in einem congenitalen missbildeten Herzen mit Bemerkungen über Endocarditis, Deutsche med. Wchnschr. 15: 148-149, 1889. 24 f.
283. Summons, W. H. *vide* 174. Case 8, 2¼ f.
284. Young, A. H. & Robinson, Arthur. Some malformations of the human heart, Med. Chronicle (Manchester) 47: 96-106, 1907-08. Case 4, 20 mo. m.

3. *Cor biloculare—9 cases*

285. Abbott, M. E. & Weiss, Edward. Diagnosis of congenital cardiac disease. In Blumer's bedside diagnosis. Phila., Saunders, 1928. v. 2, pp. 353-514. Obs. 15, 8½ mo. m.
286. Farre, J. R. On malformations of the human heart. Lond., Longman, 1814. xv, 46 pp. Case 1, 78 hr. m.
287. Forster, J. C. A heart consisting of only two cavities, Tr. Path. Soc. Lond. 1: 48-49, 1848. 78 hr. m.
288. Hastings, W. S. Cor biloculare with atresia of the aorta, J. Tech. Methods 12: 194-198, 1929. 6 days f.
289. Krausse, O. Ein Beitrag zur Lehre von den kongenitalen Herzfehlern und ihrer Koinzidenz mit andern Missbildungen, Jahrb. f. Kinderh. 62: 43-49, 1905. 14 days m.
290. Ramsbotham, F. H. The heart of an infant consisting of only one auricle and ventricle, Tr. Path. Soc. Lond. 1: 48, 1848. 10 days.
291. *Rosenthal. Munich thesis, 1898. Newborn f.

*Not verified.

292. Rudolf, R. D. A case of cor biloculare, J. Anat. & Physiol. 34: xvii-xx, 1899-1900. 16 f.
293. Wood, R. H. & Williams, G. A. Primitive human hearts; cor "biloculare" and triloculare, Am. J. Med. Sci. 175: 242-255, 1928. 15 f.

4. *Incomplete double heart—10 cases*

294. Cassel. Ueber Missbildungen am Herzen und an den Augen beim Mongolismus der Kinder, Berlin. klin. Wchnschr. 54: 159-162, 1917. 3 mo. m.
295. Dublizkaja, Olga. Zur Casuistik der Defekte der Scheidewand des Herzens, Zurich thesis, 1906. 50 pp. Case 1, 3½ m.; case 2, 2 mo.
296. Gunn, F. D. & Dieckmann, J. M. *vide* 267. Case 1, 1 f.
297. Planchu & Gardère. Un cas de cyanose congénitale avec malformations cardiaques multiples, Arch. de méd. d'enf. 12: 201-208, 1909. 2½ mo. m.
298. Robson, G. M. Congenital heart disease; a persistent ostium atrioventriculare commune with septal defects in a Mongolian idiot, Am. J. Path. 7: 229-236, 1931. 4¾ f.
299. Shattock, S. G. Malformation of the heart in a child at full term, Tr. Path. Soc. Lond. 35: 124-127, 1884.
300. Symington. On a specimen of a heart with incomplete interauricular and interventricular septa, one auriculoventricular opening (left) and a single arterial orifice (aortic), J. Anat. & Physiol. 34: xiv-xvii, 1899-1900. 3 m.
301. Turner, F. C. Malformed heart with an undivided auriculoventricular aperture, and a left superior vena cava, Tr. Path. Soc. Lond. 43: 30-31, 1892. 14 mo.
302. Wright, J. A. & Drake, A. K. A case of extreme malformation of the heart, Tr. Ass. Am. Physicians 18: 272-274, 1903. 10½ mo. m.

VIII. DEFECTS OF AORTIC SEPTUM

1. *Persistent truncus (complete defect)—21 cases*

303. Abbott, M. E. *vide* 108. 2 cases v. 4, pp. 280-281, 2½ mo., 5.
304. Buchanan, George. Malformation of heart. Undivided truncus arteriosus. Heart otherwise double, Tr. Path. Soc. Lond. 15: 89-91, 1864. 6½ mo. f.
305. Crisp, Edward. Malformation of the heart consisting in an imperfect separation of the two ventricles, with absence of the pulmonary artery, Tr. Path. Soc. Lond. 1: 50-51, 1848. 12 f.
306. Dickson, W. E. C. & Fraser, John. A congenital abnormality of the heart and blood vessels, J. Anat. & Physiol. 48: 210-214, 1913-14. 4 mo. m.
307. Feller, A. Zur Kenntnis der angeborenen Herzkrankheiten; Trunkus arteriosus communis persistens und seine formale Entstehung, Virchow's Arch. f. path. Anat. 279: 869-910, 1930-31. Case 1, 2 days f.; case 4, 2½ mo. f.
308. Finley, K. H. A congenital anomaly (truncus arteriosus communis with subacute endocarditis), Am. J. Path. 6: 317-324, 1930. 22 f.
309. Green, T. H. Malformation of heart; absence of pulmonary artery; aorta springing from right ventricle; incomplete septum ventriculorum; patent foramen ovale, Tr. Path. Soc. Lond. 19: 188, 1868. 3 mo. m.
310. Hand, Alfred. Report of a case of congenital heart disease—defect of the ventricular septum and absence of the pulmonary artery—symptoms of angina pectoris, Arch. Pediat. 26: 368-371, 1909. 3 m.
311. Peacock, T. B. & Reed, W. C. Malformation of the heart; absence of pulmonary artery, Tr. Path. Soc. Lond. 31: 91-92, 1880. 13 mo. m.
312. Pezzi, C. & Agostoni, G. Considérations cliniques anatomiques et radiologiques à propos d'un cas de maladie congénitale du coeur contrôlée à l'autopsie; persistance du tronc artériel commun, Arch. d. mal. du coeur 21: 19-29, 1928. 17 m.
313. Power, Henry & Heath, Christopher. Case of opening in septum ventriculorum, pulmonary artery and aorta given off from the heart as one trunk, Tr. Path. Soc. Lond. 16: 62-63, 1865. 24 m.
314. Prisz, H. Beiträge zur Lehre von den angeborenen Herzanomalien, Beitr. z. path. Anat. u. z. allg. Path. 7: 245-298, 1890. 9 hr. f.
315. Richardière & Huber. Inocclusion de la cloison interventriculaire avec absence d'artère pulmonaire, Bull. Soc. pédiat. de Paris 14: 29-31, 1912. 15 mo. f.
316. von Rokitansky, C. F. Ueber einige der wichtigsten Krankheiten der Arterien. Vienna, k. k. Hof- und Staatsdruckerei, 1852. 72 pp. Repr. from Denkschr. d. k. Akad. d. Wissensch. 4. Case 4, newborn.

317. Shapiro, P. F. Detorsion defects in congenital cardiac anomalies, Arch. Path. 9: 54-68, 1930. Case 1, 14 mo. m.
318. Thérемin, Émile. Études sur les affections congénitales du coeur. Paris, Asselin & Houzeau, 1895. viii, 162 pp. Obs. 96, 4 m.; obs. 97, 4.
319. Wirth, Amandus. Ein Fall von totaler Persistenz des Truncus arteriosus communis, Giessen thesis, 1912. 32 pp. 1 hr. m.
320. Zimmerman, H. M. Congenital anomaly of heart; truncus arteriosus communis, Am. J. Path. 3: 617-622, 1927. 25 m.

2. Communication between aorta and pulmonary artery—10 cases

321. Baginsky, B. Berlin. klin. Wchnschr. 16: 439, 1879. 4 m.
322. Caesar, Julius. Case of malformation of heart and abscess of brain; unusual contents, Lancet 2: 768, 1880. 9 m.
323. Elliotson. Case of malformation of the pulmonary artery and aorta, Lancet 1: 247-248, 1830-31. "Young" f.
324. Fisher, Theodore. A specimen of congenital heart disease showing vegetations of the pulmonary and aortic valves, Rep. Brit. Soc. Study Dis. Child. 2: 155-156, 1901-02. 4 mo. f.
325. Fraentzel, O. Ein Fall von abnormer Communication der Aorta mit der Arteria pulmonalis, Virchow's Arch. f. path. Anat. 43: 420-426, 1868. 25 m.
326. Gerhardt, Carl. Lehrbuch der Kinderkrankheiten; 4th ed. Tübingen, Laupp, 1881. 785 pp. Case p. 249, 5 mo. f.
327. Girard, Ernst. Ueber einen Fall von congenitaler Communication zwischen Aorta und Arteria pulmonalis, Zurich thesis, 1895. 29 pp. 37 m.
328. Hektoen, Ludvig. Rare cardiac anomalies; congenital aortico-pulmonary communication between the aorta and the left ventricle under a semilunar valve, Tr. Chicago Path. Soc. 4: 97-113, 1902. Case 1, infant m.
329. Moorhead, T. G. & Smith, E. C. Congenital cardiac anomaly—abnormal opening between aorta and pulmonary artery, Irish J. Med. Sci. 1: 545-549, 1922-23. 48 m.
330. Wilks, Samuel. Communication between the pulmonary artery and aorta, Tr. Path. Soc. Lond. 11: 57-58, 1860. 8 mo. f.

3. Congenital aneurysm of right aortic sinus—12 cases

331. Abbott, M. E. Clinical and developmental study of a case of ruptured aneurysm of the right anterior aortic sinus of Valsalva. In Contributions to medical and biological research, dedicated to Sir William Osler. N. Y., Hoeber, 1919. v. 2, 899-914, 36 m.
332. Beck, T. S. Case of aneurism of the ascending aorta, bursting into the right ventricle: with a communication between the two ventricles, Med.-Chir. Tr. (Lond.) 25: 15-20, 1842. 31 m.
333. Charteris. Notes of a case of congenital malformation of the heart; opening between aortic valve and right ventricle, Med. Press 35: 354, 1883. 53 m.
334. Goehring, Carl. Congenital aneurysm of the aortic sinus of Valsalva, J. Med. Research 42: 49-59, 1920-21. 26 m.
335. Hart, Karl. Ueber das Aneurysma des rechten Sinus Valsalvae der Aorta und seine Beziehungen zum oberen Ventrikelseptum, Virchow's Arch. f. path. Anat. 182: 167-178, 1905. Case 1, 41 m.; case 3, 23 m.
336. Jacobi, Mendel & Heinrich, Abraham. Congenital aorticoventricular fistula with engrafted acute suppurative endocarditis, Am. J. Med. Sci. 186: 364-372, 1933. 1½ m.
337. Kraus, Fr. Ueber wahres Aneurysma des Sinus Valsalvae aortae dexter, Berlin. klin. Wchnschr. 39: 1161-1164, 1902. 27 m.
338. von Krzywicki, C. Das Septum membranaceum ventriculorum cordis, sein Verhältniss zum Sinus Valsalvae dexter Aortae und die aneurysmatischen Veränderungen beider, Beitr. z. path. Anat. u. z. allg. Path. 6: 463-484, 1889. Case 4, 20 f.
339. Rickards, Edwin. Six cardiac and vascular cases, Brit. Med. J. 2: 71-72, 1881. Case 2, 30 m.
340. Thurnam, John. On aneurisms, and especially spontaneous varicose aneurisms of the ascending aorta, and sinuses of Valsalva, Med.-Chir. Tr. (Lond.) 23: 323-384, 1840. Case 7, 33 m.
341. White, W. H. A case of patent ventricular septum, together with an aneurysm of the base of the aorta opening into the right ventricle, Tr. Path. Soc. Lond. 43: 34-36, 1892. 15 m.

IX. TRANSPOSITION OF ARTERIAL TRUNKS

1. *Dextroposition of aorta*

a) *Aorta from left ventricle, ventricular septum entire—1 case*

342. McGill Museum. 39 f.

b) *Aorta from both ventricles—7 cases*

343. Abbott, M. E. *vide* 215. Case 1, 33 m.
344. Baumgartner, E. A. & Abbott, M. E. Interventricular septal defect with dextroposition of aorta and dilatation of the pulmonary artery ("Eisenmenger complex") terminating by cerebral abscess, Am. J. Med. Sci. 177: 639-708, 1929. 20 m.
345. Dalrymple, John. Diseased heart, in which the root of the aorta had an opening common to the two ventricles, Tr. Path. Soc. Lond. 1: 58-59, 1848. 25 f.
346. Eisenmenger, Victor. Die angeborenen Defecte der Kammerscheidewand des Herzens, Ztschr. f. klin. Med. (Supp.) 32: 1-28, 1897. 32 m.
347. Kurtz, C. M., Sprague, H. B. & White, P. D. Congenital heart disease, Am. Heart J. 3: 77-90, 1927-28. Case 2, 14 f.
348. McGill Museum. 15 mo. f.
349. Schramm, H. G. Schwere Herzmissbildungen bei älteren Individuen, Beitr. z. path. Anat. u. z. allg. Path. 82: 152-162, 1929. 48.

c) *Aorta from right ventricle—3 cases*

350. Summons, W. H. *vide* 174. Case 9, 13 wk.; case 10, 1.
351. Variot, G. Sur l'indépendance des malformations congénitales du coeur et de la cyanose, J. de clin. et de thérap. inf. 5: 381-386, 1897. 13 mo. m.

d) *Aorta from right ventricle, double conus—1 case*

352. Spitzer, Alexander. Ueber den Bauplan des normalen und missbildeten Herzens, Virchow's Arch. f. path. Anat. 243: 253-261, 1923. Case 10, newborn f.

2. *Complete transposition*

a) *Closed ventricular septum—32 cases*

353. Abbott, M. E. & Dawson, W. T. The clinical classification of congenital cardiac disease, Internat. Clin. 4: 156-188, Dec., 1924. Case p. 181, 7 days f.
354. von Bókay, Zoltán. Ueber Transposition der grossen Schlagadern des Herzens, Arch. f. Kinderh. 55: 321-328, 1911. 9 mo.
355. Cockle, John. A case of transposition of the great vessels of the heart, Med.-Chir. Tr. (Lond.) 46: 193-205, 1863. 2⅓.
356. Dorning, J. A case of transposition of the aorta and pulmonary artery, with patent foramen ovale; death at ten years of age, Tr. Am. Pediat. Soc. 2: 46-50, 1890. 10 m.
357. Ellis, A. G. *vide* 36. Case 2, 34 days m. *Also* Am. J. Obst. 52: 847-858, 1905.
358. Emanuel, J. G. Three specimens of congenital deformity of the heart, Rep. Soc. Study Dis. Child. 6: 240-241, 1906. Case 2, 11 m.
359. Freudenthal, Poul. Ein Fall von Transpositio aortae et a. pulmonalis (Typus IIIb Spitzer), Virchow's Arch. f. path. Anat. 266: 641-646, 1927-28 9 days m.
360. Johnson, C. P. Cyanosis, produced by transposition of the orifices of the aorta and pulmonary artery, Am. J. Med. Sci. 20: 370-374, 1850. 2 mo. m.
361. Kato, Katsuji. Congenital transposition of cardiac vessels, Am. J. Dis. Child. 39: 363-385, 1930. Case 2, 2 mo. m.; case 4, 3 wk. m.; case 5, 11 days m.
362. Kelly, Charles. Malformation of the heart; transposition of the great vessels; cyanosis, Tr. Path. Soc. Lond. 22: 92-94, 1871. 3 mo.
363. Macgregor, A. R. Cases of congenital cardiac defect in children, Edinburgh Med. J. 32: 72-75, 1925. 4 wk. f.
364. Meyer, Hermann. Ueber die Transposition deraus dem Herzen hervortretenden grossen Arterienstämme, Virchow's Arch. f. path. Anat. 12: 364-385, 1857. 4 wk.
365. Moore, R. A. Transposition of great arterial trunks, J. Tech. Methods 12: 184-186, 1929. 17 days f.
366. Opperman, Ernst. Zwei seltene anomalien der grossen Gefässstämme, Kiel thesis, 1886. 21 pp. 5 wk. m.
367. Owen, S. A. & Kingsbury, A. N.: Diagnosis of congenital heart disease in the newborn, including a record of cases of fetal endocarditis and maldevelopment, Brit. J. Child. Dis. 21: 161-172, 1924. Case 2, 2 days m.

368. Pye-Smith, P. H. Transposition of the aorta and pulmonary artery, Tr. Path. Soc. Lond. 23: 80-83, 1872. 14 wk. m.
369. Ramm, F. H. T. Zur Casuistik der Transposition dér grossen arteriellen Gefässe des Herzens, Kiel thesis, 1899. 14 pp. 56 days m.
370. Théremin, Émile. *vide* 318. Obs. 28, 29, 31-34, under 15 days; obs. 30, 2 mo.; obs. 35, 18 days m.; obs. 36, 7 mo. m.; obs. 37, 7 wk. m.; obs. 38, 44 days f.; obs. 39, 2½ mo. m.
371. Ward, Ogier. Transposition of the aorta and pulmonary artery, Tr. Path. Soc. Lond. 3: 63-65, 1852. 18 days.

b) *Defect of ventricular septum—17 cases*

372. Bissell, W. W. Remarks accompanying a demonstration of two hearts with patent interventricular septum, extensive shortening of the colon and ulceration (lues?) and huge calculus, dilatation of the ductus pancreaticus Wirsungi, Tr. Chicago Path. Soc. 9: 159-169, 1915. Case 2, infant m.
373. Buchanan, George. Malformation of the heart. Cyanosis, Tr. Path. Soc. Lond. 8: 149-150, 1857. 4 m.
374. Cautley, Edmund. Congenital heart disease; transposition of the aorta and the pulmonary artery, Proc. Roy. Soc. Med. 2, pt. 1, Sect. Dis. Child.: 162-163, 1909. 11 mo.
375. Guttman, P. Mehrfache angeborene Missbildungen am Herzen, Deutsche med. Wchnschr. 19: 84, 1893. 2 m.
376. Heuyer & Campergue. Deux cas de cyanose congénitale permanente avec autopsie, Bull. et mém. Soc. anat. de Paris 88: 209-211, 1913. Case 1, 8 m.
377. Kato, Katsuji. *vide* 361. Case 1, 1 m.; case 3, 5 wk. f.
378. Keith, Arthur. Six specimens of abnormal heart, J. Anat. & Physiol. 46: 211-214, 1911-12. Case 5, 16.
379. Lees, D. B. Case of malformed heart with transposition of aorta and pulmonary artery, Tr. Path. Soc. Lond. 31: 58-62, 1880. 7 mo. m.
380. Peacock, T. B. Transposition of aorta and pulmonary artery, Tr. Path. Soc. Lond. 33: 49-50, 1882. 7 mo. m.
381. Poltorzycka, S. & Cieszynski, F. K. Un cas de malformations multiples congénitales du coeur, Arch. de méd. d'enf. 28: 170-176, 1925. 2½ mo. m.
382. Rolly. Zur Casuistik der Transposition der grossen arteriellen Gefässe des Herzens, Jahrb. f. Kinderh. 50: 241-257, 1899. 8 mo. m.
383. Theile, F. H. On a case of congenital cardiac malformation, J. Anat. & Physiol. 37: xliv-l, 1902-03. 3½ m.
384. Théremin, Émile. *vide* 318. Obs. 44, 1 mo. f.
385. Variot & Morancé. Transposition artérielle—cyanose congénitale sans souffle, Bull. Soc. pédiat. de Paris 13: 337-340, 1911. 3 mo. m.
386. Watton, Walter & Abbott, M. E. Parasitic thoracopagus with cardiac anomaly in the host (cor biatriatum triloculare, transposition of arterial trunks and patent ductus arteriosus), Bull. Int. Ass. Med. Museums 8: 165-176, 1922. 14 mo.
387. Young, A. H. & Robinson, Arthur. *vide* 284. Case 2, 2½ f.

3. *Partial transposition—16 cases*

388. Crisp, Edward. Heart consisting of a single auricle and ventricle, Tr. Path. Soc. Lond. 1: 49-50, 1848. 10 wk.
389. Crocker, H. R. Congenitally malformed heart in a girl aged thirteen; transposition of pulmonary artery and superior vena cava; incomplete septum ventriculorum; patent foramen ovale; constriction of pulmonary artery and mitral orifice. Aorta arises from the left ventricle, but receives blood mainly from the right. Ductus arteriosus is closed, Tr. Path. Soc. Lond. 31: 92-93, 1880. 13 f.
390. Elliot, Robert. Case of univentricular or tricoelian heart, J. Anat. & Physiol. 11: 302-306, 1876-77. 19 m.
391. Grävinghoff, W. Anfallsweise Cyanose bei angeborenem Herzfehler. Monatschr. f. Kinderh. 35: 237-251, 1927. 1½ m.
392. Lebert. Ueber einen Fall von Ursprung der Aorta aus dem rechten Ventrikel neben der Arteria pulmonalis mit offenbleiben des eirunden Loches, sowie der Kammerscheidewand, ohne Cyanose, und Erhaltung des Lebens bis zum zwanzigsten Jahre, Virchow's Arch. f. path. Anat. 28: 405-414, 1863. 20 m.
393. Loehte. Ein Fall von Situs viscerum irregularis, nebst einem Beitrag zur Lehre von der Transposition der arteriellen grossen Gefässstämme des Herzens, Beitr. z. path. Anat. u. z. allg. Path. 24: 187-222, 1898. 17 m.

394. Rheiner, G. Ueber zwei Fälle angeborner Herzfehlen, Virchow's Arch. f. path. Anat. 146: 540-546, 1896. Case 1, 8 mo. f.
395. Shapiro, P. F. *vide* 317. Case 2, 2 mo. f.; case 3, 5 wk. m.
396. Théremin, Émile. *vide* 318. Obs. 40, 26 days f.; obs. 41, 16 days m.; obs. 42; obs. 43, 2 mo.; obs. 45, 12 days m.
397. Tooth, H. H. Case of origin of the aorta from the infundibulum, and of the pulmonary artery from the sinus of the right ventricle, Tr. Path. Soc. Lond. 35: 127-130, 1884. 8 m.
398. Turner, F. C. Malformed heart, consisting of two cavities, Tr. Path. Soc. Lond. 34: 32-34, 1883. 15 mo. m.

4. *Corrected transposition—4 cases*

399. Meinertz, J. Ein ungewöhnlicher Fall von angeborener Missbildung des Herzens, Virchow's Arch. f. path. Anat. 166: 385-403, 1901. 24 m.
400. Théremin, Émile. *vide* 318. Obs. 46, 4½ mo. m.; obs. 47, 9 wk. f.
401. Tönnies, Albert. Ueber eine seltene Missbildung des Herzens (Transposition der grossen arteriellen Gefässe mit Defect im hinteren Theile der Kammerscheidewand), Göttingen thesis, 1884. 61 pp. 21 m.

X. PULMONARY STENOSIS

1. *With closed septa—9 cases*

402. Abbott, M. E. *vide* 108. Case 2, 10½ m.
403. Bishop, L. F. Jr. & Wallace, S. C. Pulmonary stenosis with bacterial endocarditis in an adult, Am. Heart J. 5: 238-242, 1929-30. 32 f.
404. Clarke, J. J. A case of ulcerative endocarditis associated with stenosis of the conus arteriosus and affecting chiefly the pulmonary valve, with ulceration of the main pulmonary artery, Tr. Path. Soc. Lond. 44: 29-30, 1893. 21 f.
405. Hebb, R. G. Stenosis of pulmonary artery; congenital heart disease, Tr. Path. Soc. Lond. 41: 57, 1890. 45 m.
406. Ogle, J. W. Abnormal condition of the valve at the root of the pulmonary artery, with consequent hypertrophy of the parietes of the right ventricle of the heart, Tr. Path. Soc. Lond. 5: 69-71, 1854. 14 f.
407. Ormerod, J. A. Disease of the pulmonary valve, Tr. Path. Soc. Lond. 44: 30, 1893. 24 m.
408. Peacock, T. B. Contraction of the orifice of the pulmonary artery from fusion of the valves, Tr. Path. Soc. Lond. 10: 107-108, 1859. 23 m.
409. — —. Case of stenosis of the pulmonary artery from disease of the valves, probably of congenital origin, Tr. Path. Soc. Lond. 30: 258-262, 1879. 13 m.
410. *Reid. Munich thesis, 1896. 23 f.

2. *With patent foramen ovale, closed ventricular septum—16 cases*

411. Abbott, M. E., Lewis, D. S. & Beattie, W. W. Differential study of a case of pulmonary stenosis of inflammatory origin (ventricular septum closed) and two cases of (a) pulmonary stenosis and (b) pulmonary atresia of developmental origin with associated ventricular septal defect and death from paradoxical cerebral embolism, Am. J. Med. Sci. 165: 636-659, 1923. Case 1, 14 f.
412. Andrew, James. Congenital malformation of the pulmonary valves, Tr. Path. Soc. Lond. 16: 81-82, 1865. 6 f.
413. Ballet, Gilbert. Des abcès du cerveau consécutifs à certaines malformations cardiaques, Arch. gén. de méd. 1: 659-667, 1880. Case 2, 57 f.
414. Barlow, Thomas. Congenital heart disease; pulmonary stenosis, with dilated pulmonary artery above the stenosis, Tr. Path. Soc. Lond. 30: 272-273, 1879. 4 f.
415. Cassel. Ein Herz. Berlin. klin. Wchnschr. 28: 1221, 1891. 11 f.
416. Finlay, D. W. Malformation of the heart; stenosis of the pulmonary valve, with dilatation of the pulmonary artery and hypertrophy of the right ventricle; patency of the foramen ovale, with a cribriform opening in the septum of the auricle (ductus arteriosus closed), Tr. Path. Soc. Lond. 30: 262-265, 1879. 23 f.

*Not verified.

417. Gaines, L. M. Stenosis of the pulmonary valve of the heart with tuberculosis of the lungs as a secondary and terminal complication, Charlotte Med. J. 67: 228-230, 1913. 15 f.
418. Lafitte, Ad. Rétrécissement infundibulaire de l'artère pulmonaire d'origine congénitale; obliteration incomplète du trou de Botal; absence de cyanose; endocardite végétante au niveau du rétrécissement, Bull. Soc. anat. de Paris 67: 13-17, 1892. 17½ m.
419. McPhedran, Harris. Pulmonary stenosis; patent foramen ovale; acute endocarditis; hemiplegia, St. Michael's Hosp. Med. Bull. (Toronto) 1: 62-67, 1924. 23 m.
420. Niergarth, Wilhelm. Ein Fall von hochgradiger angeborener Stenose des Ostium arteriosum dextrum. Tod durch Lungentuberkulose, Munich thesis, 1889. 23 pp. 21 f.
421. Peacock, T. B. Contraction of the orifice of the pulmonary artery, and communication between the cavities of the auricles by the foramen ovale, Tr. Path. Soc. Lond. 1: 200-203, 1848. 20 m.
422. Saundby, Robert. Case of pulmonary stenosis with patent foramen ovale, Brit. Med. J. 2: 378-379, 1877. 11 m.
423. Seremini, P. & Montes-Pareja, J. Un cas de rétrécissement de l'artère pulmonaire avec propagation du souffle aux vaisseaux du cou sans communication inter-ventriculaire, Rev. méd. del Uruguay 27: 345-352, 1924. *Abst.* Arch. d. mal. du coeur 18: 305-307, 1925. 21 f.
424. Tuley, H. W. & Moore, J. W. Report of a case of congenital endocarditis with vegetative inflammation of the pulmonary artery and valve, Am. J. Dis. Child. 13: 426-437, 1917. 13 m.
425. Walsham, Hugh. Stenosis of the pulmonary orifice of the heart, Tr. Path. Soc. Lond. 47: 25-26, 1896. 18 f.
426. Wilks, Samuel. Malformation of the pulmonary veins, Tr. Path. Soc. Lond. 10: 79-80, 1859. 18 f.

3. With closed foramen ovale, defect ventricular septum—51 cases

427. Abercrombie, John. Congenital imperfection of septum ventriculorum with antemortem thrombosis of right ventricle and pulmonary artery, Tr. Path. Soc. Lond. 32: 73-74, 1881. 3½ m.
428. Allis, O. H. Malformation of the heart, in which there was stenosis of the pulmonary artery, perforation of the ventricular septum, and dilatation of the right ventricle, Tr. Path. Soc. Philadelphia 4: 113, 1874. 18 m.
429. Andrewes, F. W. Two specimens of rare forms of congenital malformation of the heart, Tr. Path. Soc. Lond. 54: 144-146, 1903. Case 2, 28.
430. Ballet, Gilbert. *vide* 413. Case 3, 9½ m.
431. Bayer, Josef. Zur Casuistik der Defecte im Septum ventriculorum bei scheinbar weiter Lungenarterienbahn und compensatorischer Hypertrophie der Lungenarterienäste, Giessen thesis, 1895. 34 pp. *Abst.* Centralbl. f. allg. Path. 8: 826-827, 1897. Adult f.
432. Bennetz, Ernst. *vide* 256. Case 1, 1¼ m.
433. Bissel, W. W. *vide* 372. Case 1, 22 m.
434. Blechmann, Germain & Paulin, André. Anéurisme de l'artère pulmonaire par endocardite aiguë greffée sur une cardiopathie congénitale chez une enfant, Arch. d. mal. du coeur 15: 472-480, 1922. 7 f.
435. Campergue, Berthe. *vide* 51. Case 2, f.
436. Charlone, Rogelio, Volpe, Alejandro & Reyes, F. N. Tetratología de Fallop [sic], Arch. de pediat. del Uruguay 1: 373-375, 1930. 13 m.
437. Children's Memorial Hospital (Montreal) Museum. 7 f.
438. Cochez, A. Rétrécissement de l'infundibulum de l'artère pulmonaire et communication interventriculaire sans troubles fonctionnels appréciables jusqu'à l'âge de vingt-six ans; cyanose; tuberculose pulmonaire, Bull. et mém. Soc. méd. des hôp. de Paris 13: 420-423, 1896. Adult.
439. Dickinson, Lee. Thrombosis of the pulmonary artery in a case of congenital stenosis of the orifice, Tr. Path. Soc. Lond. 48: 57-58, 1897. 4½ m.
440. Emanuel, J. G. *vide* 358. Case 3, 7 m.
441. Fallot, A. Contribution à l'anatomie pathologique de la maladie bleue (cyanose cardiaque), Marseille méd. 25: 138-158, 1888. Case 3, 36 m.
442. Hare, C. J. Malformation of the heart. Contraction of the pulmonary orifice with an opening in the septum ventriculorum, Tr. Path. Soc. Lond. 11: 45-46, 1860. 2 mo. m.
443. Hebb, R. G. Defect of cardiac septum, etc. (interventricular); congenital heart disease, Tr. Path. Soc. Lond. 41: 58, 1890. 5 f.

444. Herzog. [Ein Fall] von angeborener Pulmonalstenose mit Rechtslage der Aorta, München. med. Wchnschr. 66: 1097-1098, 1919. Same case 10 years earlier also reported by Mohr. München. med. Wchnschr. 59: 2315, 1912. 38 m.
445. Hewitt, Graily. Disease of the pulmonary valves in an infant; sudden death, Tr. Path. Soc. Lond. 10: 112-113, 1859. 11 days f.
446. Hutchinson, Jonathan. Malformation of the heart, from a child who had suffered from cyanosis. Imperfect septum of the ventricles. Rudimentary right ventricle, which was divided into two chambers by a fleshy septum between its sinus and its infundibular portion, Tr. Path. Soc. Lond. 5: 99-101, 1854. 11 f.
447. Jackson, J. B. S. Malformed heart; inter-ventricular opening, and opening of the ductus arteriosus into the arteria innominata, Boston Med. & Surg. J. 93: 449-450, 1875. 6 f.
448. Johnston, James. Cyanosis with deficiency of the interventricular septum, Brit. Med. J. 2: 351, 1872. 9 m.
449. King, Robert. Malformation of the heart associated with caries of the right mastoid bone, and abscess in the right cerebral hemisphere, Tr. Path. Soc. Lond. 23: 83-86, 1872. 4 m.
450. Kurtz, C. M., Sprague, H. B., & White, P. D. Congenital heart disease; interventricular septal defects with associated anomalies in a series of three cases examined post mortem, and a living patient fifty-eight years old with cyanosis and clubbing of fingers, Am. Heart J. 3: 77-90, 1927-28. Case 1, 23 m.
451. Moore, Norman. Two examples of malformation of the heart, St. Bartholomew's Hosp. Rep. 11: 225-230, 1875. Case 2, 8 f.
452. — —. Examples of malformation of the heart, St. Bartholomew's Hosp. Rep. 12: 101-104, 1876. Case 2, 20 f.
453. Murray, H. M. Two cases of malformation of the heart, Tr. Path. Soc. Lond. 39: 67-71, 1888. Case 2, 26 f.
454. Peacock, T. B. Malformation of the heart, consisting in contraction of the orifice of the pulmonary artery with deficiency at the base of the interventricular septum, Tr. Path. Soc. Lond. 1: 52, 1848. 2½ m.
455. — —. Contraction of the pulmonary orifice, with imperfection of the septum ventriculorum, and an osseous state of the ductus arteriosus, Tr. Path. Soc. Lond. 7: 80-83, 1856. 19 f.
456. — —. Malformation of the heart; absence of ductus arteriosus; small size of the pulmonary artery; aorta arising from both ventricles; irregular course of the aorta, etc., Tr. Path. Soc. Lond. 11: 40-43, 1860. 11½ mo. m.
457. — —. Malformation of the heart. Contraction of the orifice of the pulmonary artery, and deficiency in the septum ventriculorum. Cyanosis, Tr. Path. Soc. Lond. 13: 57-59, 1862. 9 m.
458. — —. Malformation of the heart; contraction of the infundibular portion of the right ventricle; deficiency in the septum of the ventricles, the aorta arising chiefly from the right ventricle; foramen ovale closed, Tr. Path. Soc. Lond. 17: 45-46, 1866. 7 m.
459. — —. Malformation of the heart; contraction or stenosis of the pulmonary orifice; aorta arising from both ventricles, Tr. Path. Soc. Lond. 20: 87-88, 1869. 8½ m.
460. — —. Malformation of the heart; great contraction of the pulmonic orifice; aorta arising from the right ventricle, but communicating with the left by an aperture in the septum, Tr. Path. Soc. Lond. 21: 79-80, 1870. 2½ f.
461. — —. Great contraction, or stenosis, of the pulmonary artery; defect in the septum of the ventricles and aorta arising equally from the two cavities; no ductus arteriosus; but that vessel replaced by two small branches connected with the aorta; cyanosis, Tr. Path. Soc. Lond. 22: 88-99, 1871. 17 f.
462. — —. Malformation of heart; stenosis at the commencement of the conus arteriosus of the right ventricle and at the origin of the pulmonary artery; aperture in septum ventriculorum and aorta arising partly from right side; foramen ovale and ductus arteriosus closed; cyanosis, Tr. Path. Soc. Lond. 27: 131-136, 1876. 4 f.
463. — —. Malformation of heart; great constriction or stenosis of the orifice of the pulmonary artery, aorta arising from both ventricles; defects in the fold of the foramen ovale; ductus arteriosus closed, Tr. Path. Soc. Lond. 32: 35-38, 1881. 6 m.

464. — — & Barlow, T. Malformation of the heart; stenosis of the pulmonary artery, the aorta communicating with both ventricles, Tr. Path. Soc. Lond. 31: 91, 1880. 3 m.
465. Rheiner, G. *vide* 394. Case 2, 5 f.
466. Robinson, G. C. The relation between congenital malformation of the heart and acute endocarditis, Bull. Ayer Clinic Lab. 1: 45-55, 1905. Case 1, 20 m.; Case 2, 20 m.
467. Rösler, H. Beiträge zur Lehre von den angeborenen Herzfehlern; Untersuchungen an einem Fall von Pulmonalstenose, Wien. Arch. f. inn. Med. 15: 507-520, 1928. Case 1, 7½ f.
468. Rolleston, H. D. Congenital heart disease; pulmonary stenosis; patent septum ventriculorum, Tr. Path. Soc. Lond. 43: 32-34, 1892. 20 m.
469. Scheele. Ueber congenitale Pulmonalstenose mit Kammerscheidewanddefect, Deutsche med. Wchnschr. 14: 294-297, 1888. 15 f.
470. Schmidt, J. L. O. Ueber angeborene Stenose der Arteria pulmonalis, Bonn thesis, 1892. 30 pp. 12 m.
471. Summons, W. H. *vide* 174. Case 7, 3 m.
472. Variot, G. Sur le diagnostic des affections congénitales du coeur chez les enfants, J. de clin. et de thérap. inf. 2: 329-333, 1894. 5½ mo. m.
473. — —. *vide* 351. Case 2, 5½ f.
474. Weiss, Edward. Congenital pulmonary stenosis with ventricular defect, Tr. Path. Soc. Philadelphia 44: 73-74, 1924. 17 f.
475. White, P. D. & Boyes, J. H. Subacute bacterial (streptococcus viridans) endocarditis and endocarditis involving the tricuspid valve and the pulmonary artery in a unique case of the tetralogy of Fallot complicated by congenital pulmonary regurgitation, Am. Heart J. 7: 802-807, 1931-32. 21 f.
476. — — & Sprague, H. B. Tetralogy of Fallot; case in a noted musician who lived to his sixtieth year, J. A. M. A. 92: 787-791, 1929. 60 m.

4. *With patent foramen ovale and defect ventricular septum—34 cases*

477. Abbott, M. E. *vide* 85. Case p. 730-732. *Also* 285. Obs. 11, 23 m.
478. — —, Lewis, D. S. & Beattie, W. W. *vide* 411. Case 2, 10 m.
479. Arnold, W. Der kompensatorische Kollateralkreislauf bei einem Fall von angeborener Pulmonalstenose, Centralbl. f. allg. Path. 37: 193-196, 1926. 13 m.
480. Black, D. D. *vide* 217. Case 1, 22 m. [Appears twice on chart].
481. Böhm. Fall von "angeborner Stenose des Conus arterios. pulmonal." ohne vorausgegangenen Entzundungsprozess, Berlin. klin. Wchnschr. 7: 420-423, 1870. 1¼ m.
482. Campbell, T. & Coulthard, H. L. Congenital cardiac malformation with pulmonary tuberculosis, Lancet 1: 1001-1002, 1924. 28 m.
483. Cautley, Edmund. Atresia of the conus pulmonalis, Edinburgh Med. J. 12: 257-260, 1902. 12 mo. m.
484. Crocker, H. R. Case of congenital malformation of the heart, Tr. Path. Soc. Lond. 30: 273-274, 1879. 6 f.
485. — —. Case of congenital malformation of the heart, Tr. Path. Soc. Lond. 30: 275, 1879. 2 m.
486. Cursham. Congenital malformation of the heart in a youth, Tr. Path. Soc. Lond. 7: 85-87, 1856. 18 m.
487. Fallot, A. Contribution à l'anatomie pathologique de la maladie bleue (cyanose cardiaque), Marseille méd. 25: 77-93, 1888. Case 1, 19 m.; case 2, 26 m. *cf.* 441.
488. Fox, Wilson. Cyanosis; hypertrophy of the heart, chiefly affecting the right ventricle; partial closure of the pulmonary artery by adhesion of flaps of semilunar valves; perforation of septum ventriculorum; adhesion of flaps of tricuspid valves; patent foramen ovale; closure of ductus arteriosus, Tr. Path. Soc. Lond. 19: 104-107, 1868. 3 f.
489. Freyberger, Ludwig. A case of patent septum interventriculare, patent foramen ovale, and congenital stenosis of the pulmonary artery, coupled with an anomalous distribution of the thoracic veins, Tr. Path. Soc. Lond. 49: 35-37, 1898. 11 mo. m.
490. Harrison, W. F. Congenital heart disease; extreme congenital pulmonary stenosis (tetralogy of Fallot); collateral pulmonary circulation; massive right-sided vegetative endocarditis, Am. Heart J. 5: 213-231, 1929-30. 16 f.
491. Kurtz, C. M., Sprague, H. B., & White, P. D. *vide* 450. Case 3, 11 m.

492. Leadingham, R. S. Tetralogy of Fallot; report of a case with bacterial endocarditis of the pulmonary valve and collapse of both lungs, Ann. Int. Med. 4: 620-627, 1930. 15 m.
493. Leclerc & Michel. Rétrécissement pulmonaire; communication interventriculaire; bacillose pulmonaire, Lyon méd. 122: 300-302, 1914. 21 f.
494. Mönckeberg. Pulmonalstenose, Septumdefekt, abnormer Verlauf der Aorta und frische Endocarditis, Deutsche med. Wchnschr. 35: 1044, 1909. 8 m.
495. Moore, Norman. Congenital disease of the heart, Tr. Path. Soc. Lond. 36: 176-178, 1885. 3 m.
496. Nunneley, Thomas. Aorta freely communicating with both ventricles, these with each other, small and thin-walled pulmonary artery, with very small slit-like opening into the ventricle, open foramen ovale, Tr. Path. Soc. Lond. 13: 42-44, 1862. 15 f.
497. Parker, N. Malformation of the heart; great contraction of the pulmonary orifice; aorta arising entirely from the right ventricle; aperture in the septum ventriculorum, Tr. Path. Soc. Lond. 1: 51, 1848. 13 m.
498. Peacock, T. B. Malformation of the heart; great contraction of the pulmonary orifice; deficiency in the septum ventriculorum, and open foramen ovale, Tr. Path. Soc. Lond. 5: 67-69, 1854. 6½ m.
499. — —. Contraction of the pulmonary orifice and artery with imperfection of the septum of the ventricles, and absence of the ductus arteriosus, Tr. Path. Soc. Lond. 7: 83-85, 1856. 12 mo. f.
500. — —. Malformation of the heart; contraction of the pulmonic orifice; aorta arising equally from both ventricles, Tr. Path. Soc. Lond. 21: 78-79, 1870. 8 m.
501. — —. Malformation of heart; nearly complete separation between the sinus and infundibular portion of the right ventricle; aorta arising from both ventricles, Tr. Path. Soc. Lond. 21: 83-86, 1870. 15 f.
502. Raab, Wilhelm, Weiss, Robert, Löwbeer, Bela & Rihl, Julius. Untersuchungen über einen Fall von kongenitalem Herzvitium, Wien. Arch. f. inn. Med. 7: 367-414, 1924. 15 m.
503. Reynolds, Russell. Malformation of the heart in a child. Cyanosis, Tr. Path. Soc. Lond. 8: 123-126, 1857. 13 mo. f.
504. Sanderson. Malformation of the heart, with cyanosis, Tr. Path. Soc. Lond. 10: 89-90, 1859. 6½ f.
505. Shaw, H. S. A case of congenital cardiac disease, Montreal Med. J. 32: 140-143, 1903. 12 f.
506. Siredey. Rétrécissement de l'artère pulmonaire; endocardite végétante développée sur les valvules sigmoïdes de l'artère pulmonaire; persistance du trou de Botal; communication interventriculaire, sans troubles fonctionnels, Gaz. d. hôp. civ. et mil. (Lancette franç.) 69: 521-523, 1896. 20 m.
507. Stone, W. H. A case of tricoelian heart with insufficiency of the ventricular septum, St. Thomas's Hosp. Rep. 11: 57-60, 1882. 19 f.
508. Voelcker, A. F. Congenital malformation of the heart, Tr. Path. Soc. Lond. 44: 36-37, 1893. 7½ f.

XI. PULMONARY ATRESIA

1. *With closed ventricular septum—10 cases*

509. Abbott, M. E. *vide* 190. Case 1, 9 days.
510. Abercrombie, John. Congenital atresia of right ventricle; ductus arteriosus patent, Tr. Path. Soc. Lond. 34: 78, 1883. 5 mo. f.
511. Costa, Antonio. Atresia congenita dell'ostio della polmonare, con setto interventricolare chiuso e dotto di Botallo persistente in uomo di 20 anni, Clin. med. ital. 61: 567-574, 1930. 20 m.
512. Curl, S. W. Two cases of congenital morbus cordis with atresia of the pulmonary artery and other defects, Lancet 1: 87, 1905. Case 2, 6 mo.
513. Jakubowitsch, Anna. Ein Fall von congenitaler Atresie der Arteria pulmonalis. Beitrag zur Lehre von den angeborenen Erkrankungen des Herzens, Zurich thesis, 1897. 38 pp. 3 mo. f.
514. Kugel, M. A. A clinical and pathological study of two cases of truncus solitarius aorticus (pulmonary atresia), Am. Heart J. 7: 262-273, 1931-32. Case 1, 6 mo. f.
515. Lucas, R. C. Heart from a case of cyanosis, Tr. Path. Soc. Lond. 26: 26-27, 1875. 6 days f.
516. Mautner, Hans. Beiträge zur Entwicklungsmechanik, Pathologie und Klinik angeborener Herzfehler, Jahrb. f. Kinderh. 96: 123-155, 1921. 14 days m.

517. Ogle, Cyril. Atresia of the pulmonary artery, Tr. Path. Soc. Lond. 47: 28-29, 1896. 4 mo.
518. Peacock, T. B. Malformation of the heart; obliteration of the orifice of the pulmonary artery; open foramen ovale and ductus arteriosus; cyanosis, Tr. Path. Soc. Lond. 15: 60-62, 1864. 9 days.

2. With closed foramen ovale, defect ventricular septum—12 cases

519. Abbott, M. E., Lewis, D. S. & Beattie, W. W. *vide* 411. Case 3, 11 m.
520. d'Espine & Mallet, H. Un cas de malformation congénitale du coeur avec cyanose paroxystique, Rev. de méd. 28: 941-949, 1908. 7½ mo. f.
521. von Etlinger, N. Zur Casuistik der angeborenen Herzfehler, Arch. f. Kinderh. 12: 348-360, 1890-91. 4 mo.
522. Habershon, S. H. Congenital malformation of heart and kidneys; obliteration of pulmonary artery; aorta arising from the right ventricle; imperfection of septum ventriculorum; lungs supplied from aorta by a large ductus arteriosus dividing into right and left pulmonary branches; horseshoe kidney, Tr. Path. Soc. Lond. 39: 71-74, 1888. 4 m.
523. Koller-Aeby. Zwei Fälle von Atresie der Pulmonalis, Deutsches Arch. f. klin. Med. 82: 228-240, 1905. Case 1, 4 m.
524. Kugel, M. A. *vide* 514. Case 2, 3 mo.
525. Moore, Norman. Congenital malformation of the heart, Tr. Path. Soc. Lond. 41: 55-56, 1890. 7 f.
526. Moussous, Dupérié, R., Cadenaule, Ph. & Traissac. Malformation congénitale du coeur, Arch. d. mal. du coeur 19: 540-541, 1926. 5 mo. m.
527. Peacock, T. B. Malformation of the heart—atresia of the orifice of the pulmonary artery; aorta communicating with both ventricles, Tr. Path. Soc. Lond. 20: 61-64, 1869. 13 f.
528. — —. Entire obliteration or atresia of the orifice and trunk of the pulmonary artery; cyanosis; death from cancrum oris, Tr. Path. Soc. Lond. 22: 85-88, 1871, 2¼ m.
529. Sibbald, John. Malformation of the heart, with abnormal distribution of the aortic branches to the lungs; from a child, Tr. Path. Soc. Lond. 8: 167-168, 1857. 10 wk.
530. Wheeler, Digby & Abbott, M. E. Double aortic arch and pulmonary atresia, with pulmonary circulation maintained through persistent left aortic root in a man aged twenty-nine, Canad. Med. Ass. J. 19: 297-303, 1928. 29 m.

3. With patent foramen ovale, defect ventricular septum—18 cases

531. Bach, Francis. Case of congenital morbus cordis studied over a period of twelve years, Lancet 1: 1009-1011, 1928. 30 m.
532. Baly, William. Malformation of the heart. the pulmonary artery impervious at its origin, etc., Tr. Path. Soc. Lond. 10: 90-92, 1859. 9 mo. f.
533. Chevers, Norman. Heart which displayed complete congenital obliteration of the orifice of the pulmonary artery, Tr. Path. Soc. Lond. 1: 204-205, 1848. Several wk.
534. Christeller, Erwin. Funktionelles und Anatomisches bei der angeborenen Verengerung und dem angeborenen Verschluss der Lungenarterie, insbesondere über die arteriellen Kollateralbahnen bei diesen Zuständen, Virchow's Arch. f. path. Anat. 223: 40-57, 1917. 2 m.
535. Curl, S. W. *vide* 512. Case 1, 3 mo. f.
536. Hewitt, Graily. Malformation of the heart; no cyanosis, Tr. Path. Soc. Lond. 8: 107-110, 1857. 4 mo. m.
537. Koller-Aeby. *vide* 523. Case 2, 11 mo. m.
538. Osler, William. *vide* 213. Case 3, 13 days m.
539. Peacock, T. B. Absence of the pulmonary artery, the aorta arising chiefly from the right ventricle, and giving off the pulmonary branches through the ductus arteriosus, Tr. Path. Soc. Lond. 1: 205-207, 1848. 11½ mo. m.
540. — —. Malformation of the heart; atresia of the pulmonary artery; aorta arising from right ventricle; pulmonary circulation maintained through the ductus arteriosus, Tr. Path. Soc. Lond. 25: 62-64, 1874. 11 mo. m.
541. Raeder, O. J. Congenital malformation of heart with complete obliteration of pulmonary artery, J. A. M. A. 79: 16-17, 1922. 9 days.
542. Reuben, M. S. & Steffen, W. C. A. Congenital cyanosis and congenital heart disease without murmurs, Arch. Pediat. 39: 811-818, 1922. 11 mo. m.
543. Semple, Hunter. Malformation of the heart; patent foramen ovale; imperfect septum ventriculorum; aorta given off from the right ventricle; ductus arteriosus giving off the right and left pulmonary arteries; cyanosis, Tr. Path. Soc. Lond. 21: 80-82, 1870. 10 mo.

544. Smith, Gregory. Malformation of the heart in a child, Lancet 1: 543-544, 1842. 8 mo.

545. Stewart, W. B. Atresia of the pulmonary artery in a congenitally defective heart, J. Lab. & Clin. Med. 8: 454-461, 1923. 2½ mo. f.

546. Thomson, J. & Drummond, W. B. *vide* 176. Case 5, 8½ mo. f.

547. Weiss, Salomon. Ueber einen Fall von angeborner Stenose der Pulmonalarterie, Deutsches Arch. f. klin. Med. 16: 379-392, 1875. 6 m.

548. Whipham, T. R. Pathological specimen of the heart in a case of congenital malformation, Proc. Roy. Soc. Med. 4, pt. 1, Sect. Dis. Child.: 3-5, 1911. 2.

XII. PULMONARY INSUFFICIENCY OR DILATATION

1. *Valvular insufficiency—2 cases*

549. Schwartz, S. P. & Shelling, D. H. Acquired rheumatic pulmonary stenosis and insufficiency, Am. Heart J. 6: 568-574, 1930-31. 22 f.

550. Stintzing, R. Ueber eine seltene Anomalie der Pulmonalklappen, Deutsches Arch. f. klin. Med. 44: 149-158, 1888-89. 64 f.

2. *Congenital dilatation pulmonary artery—6 cases*

551. Bristowe, J. S. Thickening and dilatation of the pulmonary artery, and its ramifications, Tr. Path. Soc. Lond. 11: 80-81, 1860. 59 m.

552. Cautley, Edmund. Congenital pulmonary regurgitation (transposition of the spleen), Brit. J. Child. Dis. 17: 187-189, 1920. 2½ mo. f.

553. Clarke, R. C., Coombs, C. F., Hadfield, G. & Todd, A. T. On Certain Abnormalities, congenital and acquired, of the pulmonary artery, Quart. J. Med. 21: 51-70, 1927-28. Case 1, 10 mo. f.; case 2, 6 mo. m.

554. Wätjen, J.: Isolierte Sklerose der Pulmonalarterie im jüngsten Kindesalter, Deutsche med. Wchnschr. 50: 713-715, 1924. 13 mo. m.

555. Wilkens, G. D. Ein Fall von multiplen Pulmonalisaneurysmen, Beitr. z. Klinik d. Tuberk. 38: 1-10, 1918. 23 f.

XIII. AORTIC STENOSIS AND ATRESIA

1. *Subaortic stenosis—12 cases*

556. Banks, J. T. Perforation of aortic valves—loud musical murmur, Dublin Hosp. Gaz. 4: 33-35, 1857. 34 f.

557. Bret & Blanc-Perducet. Le rétrécissement sous-aortique à propos d'un cas de rétrécissement sous-aortique pur, Lyon méd. 119: 261-274, 1912. 58 m.

558. Dilg, J. Ein Beitrag zur Kenntniss seltener Herzanomalien im Anschluss an einem Fall von angeborner linksseitiger Conusstenose, Virchow's Arch. f. path. Anat. 91: 193-260, 1883. 2 m.

559. Enzer, Norbert. Anomalous congenital bicuspid subaortic valve of the heart, Arch. Path. 4: 966-973, 1927. 40 f.

560. *Goldenweiser. [Pathogenesis and symptomatology of subaortic stenosis], Med. Obozr. (Moscow) 77: 319, 1912. 21 m.

561. Lauenstein, Carl. Ein Fall von Stenose des Conus arteriosus aortae, Deutsches Arch. f. klin. Med. 16: 374-378, 1875. 38 m.

562. Lindman, J. H. Ein Fall von Stenose des Conus arteriosus aortae, Deutsches Arch. f. klin. Med. 25: 510-517, 1880. 19 m.

563. Shennan, Theodore. Note on a case of double stenosis of the aortic orifice, Lancet 1: 21, 1905. 19 m.

564. Smart, Andrew. A case of double stenosis of the aortic orifice, Lancet 2: 1417-1418, 1904. 17 f. [Appears twice on chart.]

565. Thursfield, Hugh & Scott, H. W. Subaortic stenosis, Brit. J. Child. Dis. 10: 104-109, 1913. 14 m.

566. Trevor, R. S. Heart with various malformations, J. Anat. & Physiol. 36: xliv-xlv, 1901-02. 9.

2. *Aortic stenosis—11 cases*

567. Bezançon, Fernand & Azoulay, Robert. Rétrécissement congénitale de l'orifice aortique sans autre malformation cardiaque avec endocardite récente surajoutée chez une jeune fille jumelle; malformation pulmonaire et rénale associées; mort subite, Arch. d. mal. du coeur 17: 345-349, 1924. 24 f.

*Not verified.

568. Fisher, Th. Congenital aortic stenosis from a child aged four months, Rep. Soc. Study Dis. Child. 2: 16-18, 1901-02. 4½ mo. f.
569. Hare, C. J. Malformation of the heart. Obstruction at the aortic orifice (only two valves). Open ductus arteriosus, Tr. Path. Soc. Lond. 11: 46-47, 1860. 6 mo. m.
570. Laine, T. M. Heart of a child two weeks of age, with a patulous foramen ovale, a triangular opening in the ventricular septum, and a small and contracted aortic opening in which no valves could be detected, Tr. Path. Soc. Philadelphia 17: 83-84, 1894. 14 days.
571. McGill Museum. 47 days.
572. Mönckeberg, J. G. Demonstration eines Falles von angeborener Stenose des Aortenostiums, Verhandl. d. deutschen path. Gesellsch. 11: 224-229, 1907. 4 days m.
573. Mueller, Berthold. Ein Beitrag zur Kenntnis der angeborenen linksseitigen Konusverengerungen des Herzens, Virchow's Arch. f. path. Anat. 249: 368-373, 1924. Case 1, 51 hr. f.
574. Owen, S. A. & Kingsbury, A. N. *vide* 367. Case 1, 4 days m.
575. Rose, H. C. Congenital malformation of the aortic valves, Tr. Path. Soc. Lond. 24: 68-69, 1873. 13 f.
576. Stiassny, Sigmund. Ein Fall von angeborener Myocarditis fibrosa, Centralbl. f. allg. Path. 12: 417-421, 1901. 4 days m.
577. Workman, C. J. Disease of the aortic valves, in a girl aged four years, Tr. Path. Soc. Lond. 18: 54-55, 1867. 4 f.

3. *Aortic atresia—12 cases*

578. Abbott, M. E. *vide* 108. Case p. 297, 4 days f.
579. Canton, Edwin. Congenital obliteration of origin of the aorta, Tr. Path. Soc. Lond. 2: 38, 1850. 2 days f.
580. Fraser, Alexander. Two cases of congenital lesions of the heart, Proc. New York Path. Soc. 21: 91-95, 1921. Case 1, 5 days m.
581. Gauss, Harry. Congenital obliteration of the aorta, Am. J. Dis. Child. 12: 606-611, 1916. 3 days m.
582. Loeser, Alfred. Ueber kongenitale Aortenstenose und fötale Endokarditis, Virchow's Arch. f. path. Anat. 219: 309-319, 1915. 2 days f.
583. Moore, C. U. & Menne, F. R. Report of a case of congenital anomaly of the heart—reptilian, Heart 8: 297-302, 1921. 6 days m.
584. Mueller, Berthold. *vide* 573. Case 2, 5 days m.
585. Philpott, Newell. Congenital atresia of aortic ring, Ann. Int. Med. 2: 422-427, 1928-29. 62 hr. m.
586. Schrader, G. Zwei Beiträge zu den Herzmissbildungen, Centralbl. f. allg. Path. 42: 5-9, 1928. Case 1, 5 days m.
587. Shapiro, P. F. Truncus solitarius pulmonalis; rare type of congenital cardiac anomaly, Arch. Path. 10: 671-676, 1930. 4 days m.
588. Shattock, S. G. Atresia of the aortic aperture in an infant, Tr. Path. Soc. Lond. 32: 38-39, 1881. 25 days.
589. Summons, W. H. *vide* 174. Case 11, 15 wk. m.

XIV. ANOMALIES OF SEMILUNAR CUSPS

1. *Supernumerary cusps*

a) *Of pulmonary valve—8 cases*

590. Carter, C. H. Supernumerary pulmonary valve, Tr. Path. Soc. Lond. 24: 48, 1873. 1½ m.
591. Cattell, H. W. Anomalous extra cusp to the pulmonary valve, Tr. Path. Soc. Philadelphia 15: 161-162, 1891. 80 m.
592. Duckworth, Dyce. Specimen of a heart with four pulmonary valves, Tr. Path. Soc. Lond. 17: 113-114, 1866. 31 m.
593. Greenhow, E. H. Heart with four pulmonary valves and incompetency of tricuspid valve; hypertrophy of spleen, and cirrhosis of liver, Tr. Path. Soc. Lond. 20: 98-99, 1869. Adult f.
594. Jenner, William. Three specimens of malformations by excess of the pulmonary sigmoid valves, Tr. Path. Soc. Lond. 4: 102-103, 1853. Case 1, 19 m.; case 3.

595. Peacock, T. B. Two specimens, showing the condition of the heart after death from different forms of phthisis—destruction of one supra-renal capsule without bronzing—supernumerary valve at orifice of pulmonary artery, Tr. Path. Soc. Lond. 14: 126, 1863. Case 2, 46 m.
596. Wilson, J. C. Heart showing anomalous arrangement of the leaflets of the pulmonary valve, *these being four in number*, Tr. Path. Soc. Philadelphia 7: 57-58, 1878. 55 m.

b) *Of aortic valve—2 cases*

597. Abbott, M. E. On the relative incidence and clinical significance of a congenitally bicuspid aortic valve; with five illustrative cases. In Contributions to the medical sciences in honor of Dr. Emanuel Libman. N. Y., International pr., 1932. v. 1, pp. 1-38. Case 4, 31 m.
598. de Vries, W. M. Ueber Abweichungen in der Zahl der Semilunarklappen, Beitr. z. path. Anat. u. z. allg. Path. 64: 38-54, 1918. 41 m.

2. *Reduced number*

a) *Bicuspid pulmonary valve—1 case*

599. Paget, James. On obstructions of the branches of the pulmonary artery, Med.-Chir. Tr. (Lond.) 27: 162-188, 1844. Case 6, 20 f.

b) *Bicuspid aortic valve—32 cases*

600. Abbott, M. E. & Chase, W. H. Bicuspid aortic valve of congenital origin with associated defect of the interventricular septum and streptococcal endocarditis with mycotic aneurysm of left coronary artery and extensive recent infarction of myocardium of left ventricle, J. Tech. Methods 12: 171-174, 1929. 34 m.
601. Baumgartner, E. A. Bicuspid aortic valve—report of a case, Clifton Med. Bull. 8: 17-21, 1922. 39 f.
602. Déteindre, Willy. Ueber einige Fälle von zweiteilige Aortenklappen und ihre pathologische Bedeutung, Zurich thesis, 1895. 42 pp. *Abst.* Centralbl. f. allg. Path. 6: 358, 1895. Case 1, 25 m.; case 2, 42 m.; case 3, 50 m.
603. Garrod, A. E. Malformation of the aortic valves; ulcerative endocarditis; associated malformation of the liver, Tr. Path. Soc. Lond. 48: 42-45, 1897. 39 m.
604. Greenfield, W. S. Congenital malformations of the aortic valves, consisting in the existence of two segments only, Tr. Path. Soc. Lond. 27: 110-113, 1876. 68 m.
605. Lewis, Thomas & Grant, R. T. Observations relating to subacute infective endocarditis; notes on normal structure of aortic valve; bicuspid aortic valves in subacute infective endocarditis, Heart 10: 21-99, 1923. Case 1, 10 wk.; case 2, 21; case 3, 31 m.; case 4, 68 m.; case 7, 38 m.; case 8, 40 m.; case 9, 33 m.; case 10, 28 m.; case 11, 30 m.; case 12, 32 m.; case 13, 24 m.
606. Obré, Henry. Malformed aortic valves, Tr. Path. Soc. Lond. 4: 101-102, 1853. 6 wk.
607. Osler, William. On the condition of fusion of two segments of the semilunar-valves, Montreal General Hosp. Rep. 1: 233-242, 1880. Case 1, 26 m.; case 2, 20 m.; case 3, 42 m.; case 4, 42 m.; case 5, 45 m.; case 6, 40 m.; case 7, 8 mo. fetus.
608. Peacock, T. B. Case of aortic valvular disease, probably originating in malformation, etc., Tr. Path. Soc. Lond. 27: 59-67, 1876. 11 f.
609. Quain, Richard. Malformations of the aortic valves in an infant. Sudden death. Fatty degeneration (?), Tr. Path. Soc. Lond. 4: 96-99, 1853. 6 mo. m.
610. Shelby, E. P. Jr. Aortic valve with only two segments; adult heart; congenital origin, Proc. New York Path. Soc. 23-26, 1897-98. 40 m.
611. Sieveking, E. H. Atheromatous deposit, and rupture of one valve of the aorta. Congenital union of two of the valves, Tr. Path. Soc. Lond. 4: 100-101, 1853. 26 m.
612. Ucke, H. Ein Beitrag zur Casuistik der Klappenanomalien der Aorta, Virchow's Arch. f. path. Anat. 140: 206-208, 1895. 23 m.
613. Williams. Malformation of aortic valves, Tr. Path. Soc. Lond. 13: 63, 1862. 68 m.

3. *Defect*

a) *Of pulmonary valve—no cases*

b) *Of aortic valve—1 case*

614. Hektoen, Ludvig. *vide* 328. Case 2, newborn f.

XV. TRICUSPID AND MITRAL STENOSES

1. *Tricuspid stenosis—3 cases*

615. Delhaye, A. & De Groodt, A. Endocardite végétante des valvules du ventricule droit chez un adolescent porteur d'une malformation congénitale du coeur, Arch. d. mal. du coeur 20: 309-316, 1927. 16 m.

616. Peacock, T. B. Malformation of the heart. Contraction of the right auriculo-ventricular orifice with two small apertures in the septum ventriculorum, Tr. Path. Soc. Lond. 5: 64-67, 1854. 7 mo. f.

617. Stow, Bond. Congenital tricuspid stenosis complicated by mitral stenosis, Am. J. Med. Sci. 130: 329-336, 1905. 28 f.

2. *Tricuspid atresia—16 cases*

618. Barlow, Thomas. Congenital heart disease; two cases, Tr. Path. Soc. Lond. 27: 140-142, 1876. Case 1, 12 wk. f.

619. Bernstein, E. P. A case of congenital heart disease, Proc. New York Path. Soc. 6: 29-32, 1906. 2⅔ m.

620. Blackford, L. M. & Hoppe, L. D. A functionally two-chambered heart, Am. J. Dis. Child. 41: 1111-1122, 1931. 7 mo. m.

621. Cathala, Jean & Tisserand. Cyanose paroxystique par atrésie tricuspidienne, Bull. et mém. Soc. méd. d. hôp. de Paris 50: 501-505, 1926. 3 mo. f.

622. Corsdress, Otto. Ueber ein Cor biloculare bei Situs viscerum inversus, Monatschr. f. Kinderh. 28: 193-198, 1924. 4 mo.

623. Crocker, H. R. A case of congenital malformation of the heart, Tr. Path. Soc. Lond. 30: 276-277, 1879. 7 mo. m.

624. Hedinger, E. Transposition der grossen Gefässe bei rudimentärer linken Herzkammer bei einem 56jahrigen Frau, Centralbl. f. allg. Path. 26: 529-535, 1915. 56 f.

625. Hess, J. H. Congenital atresia of the right auriculoventricular orifice with complete absence of tricuspid valves, Am. J. Dis. Child. 13: 167-173, 1917. 8½ mo. m.

626. Kelly, Charles. Malformation of the heart in a case of cyanosis, Tr. Path. Soc. Lond. 19: 185-186, 1868. 5 mo.

627. Kühne, Marie. Ueber zwei Fälle kongenitaler Atresie des Ostium venosum dextrum, Jahrb. f. Kinderh. 63: 235-249, 1906. Case 1, 7 mo.; case 2, 9 mo.

628. Miller, A. J. Congenital heart disease with partial situs inversus, absence of inferior vena cava and other anomalies, Am. J. Path. 1: 467-476, 1925. 10 wk. f.

629. Moore, Norman. Congenital malformation of the heart, Tr. Path. Soc. Lond. 43: 31-32, 1892. 5 mo. m.

630. Nuhn. Ueber eine seltene fehlerhafte Bildung des Herzens, namentlich angebornen Mangel des Ostium venosum der rechten Herzkammer, Ztschr. f. ration. Med. 24: 1-11, 1865. 6 wk. f.

631. Sieveking, E. H. Congenital malformation of the heart. Absence of the right auriculo-ventricular orifice, patulous foramen ovale, defective interventricular septum, Tr. Path. Soc. Lond. 5: 97-99, 1854. 9 wk.

632. Wieland, Emil. Zur Klinik und Morphologie der angeborenen Tricuspidalatresie, Jahrb. f. Kinderh. 79: 320-343, 1914, 4 mo. f.

3. *Mitral stenosis—6 cases*

633. Carmichael, James. Congenital heart disease; patent ductus arteriosus; mitral stenosis, Edinburgh Hosp. Rep. 2: 298-303, 1894. 3 f.

634. Donnally, H. H. Congenital mitral stenosis, J. A. M. A. 82: 1318-1321, 1924. 57 hr. f.

635. Fisher, Th. Congenital mitral stenosis in a child aged fifteen months, Rep. Soc. Study Dis. Child. 2: 13-15, 1901-02. 15 mo. m.

636. Labbé, Marcel. Rétrécissement mitral pur et nanisme, Presse méd. 16: 497-499, 1908. 27 m.

637. Summons, W. H. *vide* 174. Case 14, 1½ f.
638. Willock, E. F. Rare form of congenital cardiac abnormality, Lancet 2: 1399-1400, 1923. 3 mo. m.

4. *Mitral atresia—5 cases*

639. Blackmore, Edward. Report of a singular case of malformed heart, Edinburgh Med. & Surg. J. 33: 268-273, 1830. 3½ f.
640. Lawrence, T. W. P. & Nabarro, David. A case of congenital malformation of the heart with abnormalities of abdominal viscera: absence of spleen, absence of hepatic section of inferior cava, J. Anat. & Physiol. 36: 62-75, 1901-02. 14 wk. f.
641. McIntosh, C. A. Cor biatriatum triloculare, Am. Heart J. 1: 735-744, 1925-26. 5 wk. m.
642. Théremin, Émile. *vide* 318. Obs. 106, 2 days m.
643. Wood, R. H. & Williams, G. A. *vide* 293. Case 2, 72 hr. m.

XVI. ANOMALIES OF AURICULOVENTRICULAR CUSPS

1. *Double orifices*

a) *Of tricuspid orifice—1 case*

644. Lutz, J. J. Perforate posterior tricuspid leaflet (double tricuspid orifice), Tr. Chicago Path. Soc. 13: 143-145, 1931. 43 m.

b) *Of mitral orifice—8 cases*

645. Abbott, M. E. *vide* 85. Case p. 759-760 (2nd ed. 1915, p. 407-408; 1st ed. 1910, p. 393-394), 5.
646. Camisa, G. Zwei neue Fälle von Ostium atrio-ventricular sinistrum duplex, Centralbl. f. allg. Path. 23: 1027-1031, 1912. Case 1, adult f.; case 2, 53 f.
647. Cohn, Isidor. Ueber doppelte Atrio-ventrikularostien, Königsberg thesis, 1896. 21 pp. *Abst.* Centralbl. f. allg. Path. 8: 825, 1897. 71 m.
648. Degen, K. W. A. Drei Fälle seltner Missbildungen der Herzklappen (Mitralis, Tricuspidalis, Pulmonalis), Greifswald thesis, 1903. 41 pp. 22 f.
649. Greenfield, W. S. Double mitral valve, Tr. Path. Soc. Lond. 27: 128-129, 1876. 28 m.
650. Pisenti, G. Di una rarissima anomalia della tricuspide, Ann. d. Univ. libera di Perugia. Fac. med.-chir. 3: 107-116, 1887-88. 55 m.
651. Stuhlweissenburg, O. Ostium atrioventriculare sin. duplex, Centralbl. f. allg. Path. 23: 342-348, 1912. 36 f.

2. *Insufficiency or defect*

a) *Of tricuspid valve—5 cases*

652. Abbott, M. E. & Weiss, Edward. *vide* 285. Case p. 484-485, 16 m.
653. Arnstein, Alfred. Eine seltene Missbildung der Trikuspidalklappe ("Ebsteinsche Krankheit"), Virchow's Arch. f. path. Anat. 266: 247-254, 1927. 20 f.
654. Geipel, Paul. Missbildungen der Tricuspidalis, Virchow's Arch. f. path. Anat. 171: 298-334, 1903. Case 3, 15 m.
655. Hotz, A. Ueber angeborene Trikuspidalinsuffizienz, Jahrb. f. Kinderh. 102: 1-12, 1923. Case 1, 13 f.; case 2, 12 m.

b) *Of mitral valve—2 cases*

656. Ariel, M. B. Ein seltener Fall von angeborenem Herzfehler bei einem Neugeborenen, Virchow's Arch. f. path. Anat. 277: 501-506, 1930. 2 days m.
657. Enzer, Norbert. Personal communication. 14 f.

XVII. PATENT DUCTUS ARTERIOSUS

1. *Simple patency—92 cases*

658. Abbott, M. E. *vide* 215. Case 4, 33 m.
659. de Almagro, Manuel. Étude clinique et anatomo-pathologique sur la persistance du canal artériel, Paris thesis no. 63, 1862. 120 pp. 19 f.

660. Bernutz, G. De la persistance du canal artériel, Arch. gén. de méd. 20: 415-435, 1849. 23 m.
661. Boldero, H. E. A. & Bedford, D. E. Infective endocarditis in congenital heart disease involving the pulmonary artery, Lancet 2: 747-749, 1924. 29 m.
662. Bommer, Max. Ueber offenen Ductus arteriosus Botalli, Freiburg thesis, 1900. 29 pp. 37 days m. *Also* 2 cases quoted here (original source not located), 36 m., 13 f.
663. Brooks, Clyde. Persistent patency of the ductus arteriosus Botalli in the dog, Arch. Int. Med. 9: 44-54, 1912.
664. Buchwald. Aneurysma des Stammes der Arteria pulmonalis, Deutsche med. Wchnschr. 4: 13-15, 25-28, 1878. 21 f.
665. Carpenter, George. Congenital morbus cordis—patent ductus arteriosus; aortic valves bicuspid; right heart dwarfed, Proc. Roy. Soc. Med. 2, pt. 1, Sect. Dis. Child.: 163-165, 1909. 3 mo. f.
666. — —. A fatal case of icterus neonatorum—microscopical changes in the liver, Proc. Roy. Soc. Med. 2, pt. 1, Sect. Dis. Child.: 172-177, 1909. 19 days f.
667. Caylor, H. D. Patent ductus arteriosus and saccular aneurysm of the aorta, Tr. Chicago Path. Soc. 10: 296-299, 1918. Adult f. [Same case as 695.]
668. Chessman, F. N. A congenital heart lesion, Proc. New York Path. Soc. 5: 68-72, 1905. 22 mo. m.
669. Chevers, Norman. Permanence of the ductus arteriosus, and constriction of the thoracic aorta and on the means by which the duct becomes naturally closed, Lond. Med. Gaz. 1: 187-192, 1845. Adult f.
670. Coupland, Sidney. Congenital malformation of the heart—patent ductus arteriosus, defect of the ventricular septum, cyanosis, facial erysipelas, pericarditis, death, Med. Times & Gaz. 2: 501-503, 1884. 31 m.
671. Crooks, T. T. Patent ductus arteriosus complicating acute anterior poliomyelitis, Tr. Chicago Path. Soc. 11: 361-363, 1923. 8 f.
672. Crouzet. Persistance du canal artériel. Bull. Soc. anat. de Paris 14: 323-325, 1870. 16 f.
673. Darier, J. Persistance du canal artériel chez une femme de 51 ans, Bull. Soc. anat. de Paris 60: 55-58, 1885. 51 f.
674. Drasche. Ueber einen Fall von Persistenz des Ductus arteriosus Botalli, Wien. klin. Wchnschr. 11: 1195-1197, 1898. 29 f.
675. Durno, Leslie & Brown, W. L. A case of dissecting aneurysm of the pulmonary artery; patent ductus arteriosus; rupture into the pericardium, Lancet 1: 1693-1694, 1908. 33 m.
676. Duroziez, P. Mémoire sur la persistance du canal artériel sans autre communication anormale, Compt. rend. Soc. de biol. 14: 279-292, 1862. Case 1, 40 m.
677. Fagge, C. H. Case of patent ductus arteriosus attended with a peculiar diastolic murmur, Guy's Hosp. Rep. 18: 23-30, 1873. 45 f.
678. Foulis, James. On a case of patent ductus arteriosus with aneurysm of the pulmonary artery, Edinburgh Med. J. 30: 17-33, 1883-84. 22 f.
679. Franck, François. Sur le diagnostic de la persistance du canal artériel, Gaz. hebd. de méd. et de chir. 15: 588-589, 1878. 2.
680. Garipuy. Persistance du canal artériel n'ayant entraîné aucun trouble pendant 28 ans—mort rapide à l'occasion d'un accouchement, Bull. et mém. Soc. anat. de Paris 82: 179-180, 1907. 28 f.
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2. *So-called aneurysm—13 cases*

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737. Roeder, H. Ein Fall eines solid thrombirten Dilatations-Aneurysma des Ductus arteriosus Botalli, Virchow's Arch. f. path. Anat. 166: 513-526, 1901. 10 days m.
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3. *Absence of ductus arteriosus—no cases*

XVIII. COARCTATION OF THE AORTA

1. *Adult type—70 cases*

740. Abbott, M. E. & Hamilton, W. F. Complete obliteration of the descending arch at insertion of the ductus in a boy of fourteen; bicuspid aortic valve; impending rupture of the aorta; cerebral death, Am. Heart J. 3: 381-421, 1927-28. 14 m.

741. Anderson, R. G. A case of coarctation of the aorta, St. Bartholomew's Hosp. J. 36: 18-19, 1928-29. 44 m.
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745. Bode, O. B. & Knop, F. Ueber Aorten-Isthmus-Stenose mit Beitrag zweier weiterer Fälle, Deutsches Arch. f. klin. Med. 163: 298-308, 1929. Case 1, 54 m.
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758. Jordan, F. L. J. & ter Haar, F. T. Ein Fall von volkommenem Verschluss der Aorta thoracica, Anat. Anz. 66: 24-30, 1928. Adult m.
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765. Lüttich. *vide* 736. Case 1, 26 m.
766. McGill Museum. 63 f.
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770. Moore, Norman. *vide* 452. Case 1, 57 m.
771. Muriel, William. Case of contracted aorta, Guy's Hosp. Rep. 7: 443-444, 1842. 25 m.

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775. Peacock, T. B. Open ductus arteriosus, Tr. Path. Soc. Lond. 13: 38-39, 1862. 30 m.
776. Poynton, F. J. & Sheldon, W. P. H. Coarctation of the aorta with ulcerative aortitis, Arch. Dis. Child. 3: 191-193, 1928. 8 m.
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782. Scheiber, S. H. Ueber einen Fall von Obliteration der Aorta, entsprechend dem Ductus arteriosus Botalli, Virchow's Arch. f. path. Anat. 26: 218-220, 1863. 41 m.
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785. Strassner, Horst. Ein Fall von völliger Obliteration der Aorta an der Einmündungestelle des Ductus Botalli, Deutsches Arch. f. klin. Med. 95: 344-352, 1909. 36 m.
786. Thomson, A. P. & Lamb, F. W. M. A case of coarctation of the aorta, Arch. Dis. Child. 4: 377-380, 1929. 5½ f.
787. Wadstein, Emil. Om stenos och obliteration af aorta vid eller i närheten af ductus Botalli, Lund thesis, 1897. 121 pp. 17 m.
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789. West, G. R. Case of stenosis of the aorta, Med. J. Australia 2: 195-196, 1919. 50 m.
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792. Wood, John. An injected preparation of a specimen of obliteration of the thoracic aorta, Tr. Path. Soc. Lond. 10: 97-99, 1859. Adult m.

2. *Infantile type—9 cases*

793. de Bary, J. Verengerung der Aorta an der [illegible] des Ductus Botalli, Virchow's Arch. f. path. Anat. 31: [illegible] m.
794. Chevers, Norman. Case illustrating the earliest stage of the malformation usually known as distribution of the descending aorta from the pulmonary artery, Tr. Path. Soc. Lond. 1: 55, 1848. 8 hr.
795. Fawcett, John. *vide* 749. Obs. 1, 5 mo. f.; obs. 4, 16 hr. f.
796. Lambert, R. A. Anomaly of heart and aorta; multiple defects with stenosis of aortic arch and pulmonary artery becoming descending aorta, Bull. Int. Ass. Med. Museums 8: 177-183, 1922. 20 days m.
797. Pansch, K. C. P. Ueber Stenose des Isthmus aortae mit gleichzeitiger Persistenz des Ductus arteriosus Botalli bei Neugeborenen, Giessen thesis, 1905. 36 pp. 5 days m.
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799. Rauchfuss, C. Ein Fall von Stenose der Aorta an der Einmündungsstelle des Ductus arteriosus bei einem dreiwochentlichen Kinde, Virchow's Arch. f. path. Anat. 18: 544-546, 1860. 3 wk. m.

800. Rees, G. A. The heart of a child, presenting an open state of the ductus arteriosus, Tr. Path. Soc. Lond. 1: 203-204, 1848. 10 wk. m.

3. *Pulmonary artery forms descending aorta—6 cases*

801. Barlow, Thomas. *vide* 618. Case 2, 3 mo. f.

802. Bergmann, A. Angeborene Atresie des Isthmus aortae kombiniert mit Mitralstenose bei einem fünfeinhalbjährigen Kind, Arch. f. Kinderh. 67: 44-56, 1919. 5½ f.

803. Dick, G. F. Anomalous fetus, with bipartite uterus and single fused kidney, Tr. Chicago Path. Soc. 6: 131-134, 1906. Fetus.

804. Fraser, Alexander. *vide* 580. Case 2, 6 days m.

805. Hicks, J. W. Malformation of aorta and pulmonary artery, Tr. Path. Soc. Lond. 15: 85-87, 1864. 4 days f.

806. Kohl, Ludwig. Ein Fall von kongenitaler Missbildung des Herzens, Centralbl. f. allg. Path. 20: 1089-1093, 1909. Newborn f.

XIX. HYPOPLASIA OF THE AORTA—2 cases

807. Apelt, F. Ueber die allgemeine Enge des Aorta-systems, Deutsche med. Wchnschr. 31: 1186-1189, 1905. Case 1, 20 m.; case 2, 17 m.

XX. ANOMALIES OF AORTIC ARCH

1. *Double aortic arch—5 cases*

808. Curnow, John. Double aortic arch enclosing trachea and oesophagus, Tr. Path. Soc. Lond. 26: 33-37, 1875. 87 f.

809. Hamdi. Ein seltene Aortenanomalie, Deutsche med. Wchnschr. 32: 1410-1411, 1906. 45 f.

810. Harris, H. A. A foetus presenting a combination of rare anomalies, J. Anat. & Physiol. 57: 76-95, 1922-23. 27 wk. fetus m.

811. Herrmann, Walter. Double aortic arch, Arch. Path. 6: 418-425, 1928. 6 mo. f.

812. Roschdestwenskij, K. G. Der doppelte Aortenbogen, Anat. Anz. 68: 145-151, 1929. 55 m.

2. *Right aortic arch—14 cases*

813. Annan, J. L. A case of an abnormal sinuous aorta, J. Anat. & Physiol. 44: 241-243, 1909-10. Adult.

814. Arkin, A. Totale Persistenz des rechten Aortenbogens im Röntgenbild, Wien. Arch. f. inn. Med. 12: 385-416, 1926. 50 m.

815. Combes, R. H. & Christopherson, Cecil. Transposition of the aortic arch, St. Bartholomew's Hosp. Rep. 20: 273-277, 1884. Fetus.

816. Gainer, Charles & Villemin, Fernand. Sur un cas très rare de malformation congénitale des gros vaisseaux de la base du coeur, chez un foetus humain, Compt. rend. Soc. de biol. 67: 848-849, 1909. Fetus f.

817. Ghon, A. Ueber eine seltene Entwicklungsstörung des Gefässsystems, Verhandl. d. deutschen path. Gesellsch. 12: 242-247, 1908. 4½ mo. f.

818. Gruber, Wenzel. Gefäss-, (Nerven-, und Muskel-) Anomalien—Fremde Körper, Vierteljahrsschr. f. d. prakt. Heilk. 1: 78-81, 1846. 8 days f.

819. Harris, H. A. & Whitney, Caroline. The heart of a child aged nineteen months presenting right and left aortic arches, with multiple anomalies of the heart and great vessels, Anat. Rec. 34: 221-232, 1927. 19 mo. m.

820. Hurley, L. E. & Coates, A. E. Case of right-sided aortic arch and persistent left superior vena cava, J. Anat. & Physiol. 61: 333-339, 1926-27. 53 f.

821. Jex-Blake, A. J. & Keith, Arthur. Obstruction of the oesophagus caused by a persistent ductus arteriosus, Lancet 2: 542-544, 1926. Young dog m.

822. Lockwood, C. B. Right aortic arch, Tr. Path. Soc. Lond. 35: 132, 1884. Fetus.

823. McGill Museum. 61 f.

824. Reid, D. G. Three examples of a right aortic arch, J. Anat. & Physiol. 48: 174-181, 1913-14. Case 1, adult; case 2, adult; case 3, adult.

3. *Absence aortic arch—3 cases*

825. Gaspar, I. Two of the rarer congenital anomalies of the heart, Am. J. Path. 5: 285-294, 1929. Case 1, 6 mo. f.
826. Hayashi, A. *vide* 691. Case 1, 6 days m.
827. McGill Museum. 1 day f.

4. *Right subclavian from descending aorta—5 cases*

828. Barwell, Richard. Abnormal origin of arteries from the aortic arch, Tr. Path. Soc. Lond. 18: 68, 1867.
829. Dolgopol, V. B. Anomalous origin of the right subclavian from the descending arch of the aorta, J. Tech. Methods 13: 112-118, 1934. 36 f.
830. Peacock, T. B. Aneurism of the arch of the aorta proving fatal by pressure on the left recurrent nerve; irregular origin of the large vessels, Tr. Path. Soc. Lond. 21: 134-136, 1870. 44 m.
831. Wood, John. Two specimens of abnormal origin of the right subclavian artery, Tr. Path. Soc. Lond. 10: 119-128, 1859. 2 cases.

5. *Left subclavian from ductus arteriosus or pulmonary artery—1 case*

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6. *Common brachiocephalic trunk—2 cases*

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XXI. ANOMALOUS CORONARIES

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2. *Right coronary into coronary sinus—1 case*

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3. *Aneurysm right coronary—1 case*

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XXII. ANOMALOUS PULMONARY ARTERIES—5 cases

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XXIII. ANOMALIES OF GREAT VEINS

1. *Of systemic vein (persistent left superior vena cava)—9 cases*

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XXIV. CONGENITAL ARTERIOVENOUS ANEURYSM—6 cases

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Index*

*Reference numbers are indicated following the Author's name.

ABBOTT OUTLINE FORM

During the last year of her life Dr. Abbott held a grant from the Carnegie Foundation for aid in the preparation of a proposed textbook on congenital cardiac disease. In order to facilitate the labor of compiling data on the many individual cases, assembled from the literature and from her personal experience, which formed the background for her proposed text, the accompanying outline was made and utilized, under her direction. It presents in succinct form all the information which seems to be of significance in the study of a case of congenital cardiac disease. Dr. Abbott intended to publish this form, that it might be available for the use of others preparing reviews and statistical monographs, and for the guidance of authors desiring to report individual cases. As the acknowledged authority in her field, Dr. Abbott frequently received manuscripts for criticism and revision, and she recognized the potential value of this outline as a guide to reporters. There are now in the American literature several papers published since 1940 by physicians who received this form from Dr. Abbott's office, and used it for the revision of their manuscripts.

Abbott Outline Form for Congenital Heart Disease

Age Sex Race

PATHOLOGY

Lesion

Termination: stillborn sudden death congestive failure
Cause of death: congenital heart lesion acquired valvular disease
bacterial endocarditis or endarteritis tuberculosis
cerebral vascular disease accidental operation for CHD
other causes
Autopsy: hours post mortem Parts examined:
Foetal Passages: patency of ductus arteriosus (shape:)
foramen ovale auricular septum ventricular septum
Arteries: atheroma
arteritis
Pulmonary artery: dilatation circumference diameter
hypoplasia
Aorta: dilatation circumference diameter
hypoplasia coarctation
Collateral circulation
Coronary arteries and veins
Heart: apex
transposition: atria ventricles arteries veins
hypertrophy: RA mm. RV mm. LA mm. LV mm. dilatation
weight Gm. thoracic diameter cm. heart diameter cm.
hypoplasia:
valve rings: aortic cm. pulmonary cm. mitral cm. tricuspid cm.
disease: chronic
acute

cusp anomalies:
miscellaneous notes on gross findings:
microscopic cardiac findings:
Bacteriological:
Other organs: infarcts
associated congenital anomalies

ANAMNESIS

History of cardiac illness: earliest signs (age)
first diagnosed as CHD (age)
Terminal illness: admitted (date) died (date)
chief complaint
course
Past history: maternal health during pregnancy
birth
infancy and after—infectious diseases
tuberculosis rheumatic fever
congenital syphilis syphilis
others
Family diseases: syphilis
tuberculosis rheumatic fever
alcoholism (drugs)
mongolism
parental exposure to x-ray and radium
Family history and examination
relationship of parents (diagram)
Table of patient and siblings arranged by pregnancy rank (1, 2, 3, to head the columns).

	1	2	3	4	5	6	7	8
Sex								
Miscarriage								
Stillbirth								
Premature (week)								
Full term								
Age								
Alive								
Dead								
Cause death								
Heart								
Other defects								
Health (if alive)								

Table of patient's children arranged by pregnancy rank. Patient's parents.

	1	2	3	4	5	6	Father	Mother
Sex								
Miscarriage, etc.								
Age								
Alive								
Dead								
Cause death								
Heart								
Other defects								
Health (if alive)								

Data concerning affected relatives (cousins, uncles, aunts, grandparents, etc.)

CLINICAL OBSERVATIONS

Symptoms: cyanosis (slight moderate marked terminal ; general
lips retinae) clubbing (nose extremities)
dyspnea dyspneic attacks orthopnea cough dysphonia pallor
dysphagia pain palpitation

hemorrhage: epistaxis blood in sputum frank hemoptysis other
edema ascites
menses: onset regularity
cerebral: syncopic attacks other
development: height weight remarks

Notes for prognosis: (occupation, mental development, habits, etc.)

Physical signs: *respiration* *pulse:* *rate, character*
precordial bulge pulsation
apex impulse: seen felt location
thrill: timing location
dullness: enlarged
sounds: general—
detail—*Apex* *Pulmonary* *Aortic* *Triscupid*
1.
2.
3.
murmurs: *Location* *Transmission* *First Noticed*
continuous
presystolic
systolic
diastolic
double
heart rhythm *rate*
liver
spleen
lungs
other notes

Tests: urine
syphilis: (state method used)
R. B. C. Hgb. W. B. C. Smear
Blood culture Blood pressure
X-rays: fluoroscope
orthodiagram (chest plate): heart measurements
Electrocardiography:
Other tests:

Clinical Report

A CASE OF AORTO-PULMONIC COMMUNICATION INCIDENT TO A CONGENITAL AORTIC SEPTAL DEFECT: DISCUSSION OF EMBRYOLOGIC CHANGES INVOLVED

SAMUEL G. SHEPHERD, M.D., LT. COL. FELIX R. PARK, M.C., A.U.S., AND J. RODERICK KITCHELL, M.D.
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UNTIL William B. Porter's recent article on "The Syndrome of Rupture of an Aortic Aneurysm Into the Pulmonary Artery,"[1] very little had been written on the clinical entity which exists when there is a communication between these two vessels. It is interesting to note, however, that, as early as 1835, Hope referred to two instances of rupture of an aortic aneurysm into the pulmonary artery which were reported by M. M. Payne and Zeink,[2] and Wills,[3] respectively.

In the cases reported by Porter, the communication resulted from the rupture of an aortic aneurysm, syphilitic in origin, into the pulmonary artery. Our patient, however, developed his fistulous opening between the aorta and the pulmonary artery as the result of a congenital defect. According to M. E. Abbott,[4] a defect of the aortic septum may be situated above the valves, or, more commonly, it occupies the right aortic sinus of Valsalva and directly communicates with the pulmonary conus, or the defect exists as a thin-walled aneurysmal sac which undergoes rupture in later life. Not infrequently a bulbar septal defect below the aortic cusps is also present.

Most congenital defects are caused by abnormalities in the formation of the septum which divides the heart into a right and a left side. About the fifth week of fetal life a septum between the aorta and pulmonary artery appears, and its formation is completed before the eighth week of fetal life. Concomitantly with the formation of the septum, rotation of the heart occurs, so that the aorta is placed to the left and posterior, and the pulmonary artery lies to the right and anterior. Defects ensue if there is interference with fusion of the septa, or when the heart rotates incompletely or not at all. The type and extent of the anomaly depend on the period at which the arrest occurred.

In the development of the heart the bulbus cordis becomes partially enveloped by the rapidly growing primitive atrium, and the groove against which the bulbus cordis lies is the first indication of a division into right and left atria. A subdivision into definite chambers is ac-

From the Cardiac Clinic of the Presbyterian Hospital in Philadelphia.
Received for publication April 30, 1943.

complished by the formation of a septum, the septum primum, which grows downward into the cavity to meet a septum growing from below, the septum intermedium. However, a communication is re-established between the two atria by the formation of an opening in the upper part of the septum primum, the foramen ovale. This opening persists until birth, and is closed normally by the fusion of the septum primum with the septum secundum, which grew downward from the upper wall of the atrium immediately to the right of the foramen ovale, or septum primum.

By the growth of a septum from the lower part of the ventricle, two chambers are formed. An interventricular foramen exists for a time ventrally, because the dorsal part of the septum grows more rapidly than the ventral, and joins the dorsal part of the septum intermedium above. However, closure is effected ultimately by the fusion of the aortic septum with the ventricular septum.

When, during the elongation and rotation, the developing heart assumes the S-shaped configuration, the bulbus cordis lies ventral to the primitive ventricle, so that the adjacent walls of the bulbus cordis and the primitive ventricle are in apposition. These subsequently fuse and are obliterated, thus establishing a free communication between the bulbus cordis and the right ventricle. The bulbus cordis remains separated from the left ventricle by the upward growth of the ventricular septum, and remains an integral part of the right ventricle, of which it forms the infundibulum. The bulbus cordis at the junction with the truncus arteriosus is brought ventral to, and in approximation with, the atrial canal.

The aortic septum presents itself as two ridgelike thickenings projecting into the lumen of the truncus arteriosus and bulbus cordis. These projections ultimately meet and fuse to form a septum which courses spirally toward the proximal end of the truncus arteriosus, thus dividing it into two vessels, the aorta and pulmonary artery. Proximal to the heart, the pulmonary artery lies anterior to the aorta, but they are side by side above. In the proximal portion of the aortic septum four endocardial cushions develop, and in the bulbus cordis two endocardial thickenings form. These unite to make a short septum which joins with the aortic septum above and with the ventricular septum below, thus bringing the bulbus cordis into communication with the pulmonary artery, while the left ventricle is in continuity with the aorta. The pulmonary artery communicates with the sixth pair of aortic arches, and the aorta communicates with the remaining aortic arches.

The four endocardial cushions at the proximal portion of the truncus arteriosus, namely, the anterior, posterior, and the two lateral, are subsequently affected by the development of the aortic septum, which, as it grows downward, divides the lateral thickenings into two, thus giving origin to six thickenings, the anlages of the semilunar valves, three at the aortic and three at the pulmonic orifice. Expansion of the bases of the ventricles produces an invagination at the atrioventricular por-

tion of the heart, thus forming the rudiments of the lateral cusps of the atrioventricular valves, and the downward development of the septum intermedium forms the mesial or septal walls of the cusps.

In the case we are presenting, the aortic septal defect existed as a thin aneurysmal sac which ruptured later in life, thus establishing the aorto-pulmonic communication, with the attendant physical signs of an arteriovenous shunt which are encountered in these cases. There was no evidence of the arterial wall degeneration or pressure erosion which have usually been reported in similar cases.

CASE REPORT

A. C., a Negro, aged 41 years, a chauffeur and butler, was admitted to the Presbyterian Hospital Jan. 3, 1935, complaining of severe dyspnea. He had been in apparently good health until four months previously, when he developed postprandial indigestion characterized as a "lump in the chest," with associated dyspnea. These symptoms were relieved somewhat by bisodol, essence of peppermint, and other remedies which he tried empirically. Approximately seven weeks before admission he contracted a "cold" which proved to be intractable to his treatment, so that he sought aid in the hospital's receiving ward. It was then that he was told for the first time that he had heart disease. His cold was treated effectively, and he was referred to the cardiac clinic. However, the cough and dyspnea persisted, although the cold apparently cleared up. During the year prior to his hospital admission he lost 23 pounds and became easily fatigued and dyspneic.

The past medical history was noteworthy because of frequent attacks of tonsillitis, a chancre in 1916, and, subsequently, an ulceration on the penis, at the same site, one year before his hospital admission. He had had a gonorrheal infection in 1917 and "rheumatism" in 1933. He was in the Army in 1917, and apparently there was no evidence of cardiac disease at that time. There was no familial history of heart disease or other chronic disease.

General physical examination revealed a middle-aged, cooperative, robust Negro lying in bed with only one pillow under his head, apparently comfortable except for slight dyspnea. The pupillary reflexes were normal, the mucous membranes pale, and he had herpes labialis simplex. The chest was symmetrical, and the percussion note and tactile and vocal fremitus were normal, with coarse, moist râles at the bases of the lungs. The pulse rate was regular at 118/minute; the blood pressure in the right arm was 170/85, and 155/60 in the left. The apex beat was in the fifth intercostal space outside the nipple line. There was a coarse, continuous thrill over the precordium throughout the cardiac cycle, associated with a continuous, roaring, machine-like murmur which was heard best in the aortic area and over the upper portion of the sternum. The liver was smooth and tender, and extended 8 cm. below the costal margin. There was no ascites, peripheral edema, or evidence of pulmonary osteoarthropathy. No neurological abnormalities were found. Examination of the vocal cords revealed no abnormalities.

Laboratory Studies.—The blood Wassermann and Kahn reactions were positive (4 plus). Electrocardiographic study revealed sinus tachycardia and a rate of 120. A teleoroentgenogram revealed the following cardiac measurements: Left base, 9.5 cm., right base, 6.5 cm., cardio-

thoracic ratio, 16 to 25 cm. at the level of the fifth rib, oblique diameter, 16.4 cm., transverse diameter across the auricles, 12 cm., and arch of the aorta at the level of the first anterior interspace, 5 cm. The right dome of the diaphragm was considerably higher than the left, and both pulmonary fields were very nearly filled with an extensive mottled infiltration which was fairly evenly distributed and bilaterally equal. Subsequent fluoroscopic study and a roentgenogram made in the left lateral position showed a rather unusual bulging on the anterior surface.

The patient was hospitalized for forty-nine days, during which time it was believed that he had either a dissecting aneurysm of the aorta, with rupture into the pulmonary artery, or an aneurysm of the left anterior sinus of Valsalva, with perforation into the pulmonary conus.

He was discharged improved, and sent to the cardiac clinic, and from Feb. 21, 1935, until Nov. 27, 1935, he showed but little additional improvement; he had periodic decompensation, which was remedied by bed rest, digitalis, and purine drugs. Ultimately, however, he became markedly decompensated, with pronounced cyanosis of the lips, mucous membranes, and finger tips, engorgement of the cervical veins even in the orthopneic position, severe dyspnea with frequent paroxysms of coughing, bilateral hydrothorax, hepatic engorgement with its attendant tenderness, ascites, and dependent edema. Death occurred nine months after his discharge from the hospital, on Dec. 1, 1935.

Fig. 1.—View of the defect as seen from the aortic aspect. Note the aortic valve cusps running into the defect.

Post-mortem examination revealed the following: The pericardial sac contained approximately 700 c.c. of straw-colored fluid. The heart showed a slight dextrorotation. It weighed 500 grams. In the aorta, immediately above the junction of the right posterior and the anterior leaflets, there was an opening 2 cm. in diameter which had a smooth edge. This opening connected the aorta with a sac 1.5 cm. deep and 3 cm. across. The sac bulged into the right ventricle just below the valve leaflets. In the pulmonary artery there was a small opening, 1 cm. in diameter, in the left anterior sinus of Valsalva. This opening connected the pulmonary artery with the aneurysmal sac described

above. All of the valves appeared normal except the left anterior pulmonary leaflet, which was somewhat shortened as a result of contraction around the opening in the pulmonary artery. The left ventricular wall was 1.4 cm. thick, and the right, 0.5 cm. The circumferences of the various valve orifices were as follows: aortic, 7 cm., pulmonic, 9 cm., mitral, 11 cm., and tricuspid, 12 cm. In the ascending arch of the aorta there were several scars in the media caused by fibrous tissue growth. The coronary arteries were patent and appeared grossly normal. The myocardium had a normal red color and revealed nothing unusual. The blood vessels of the heart walls were thickened. No microscopic changes were found in the aorta.

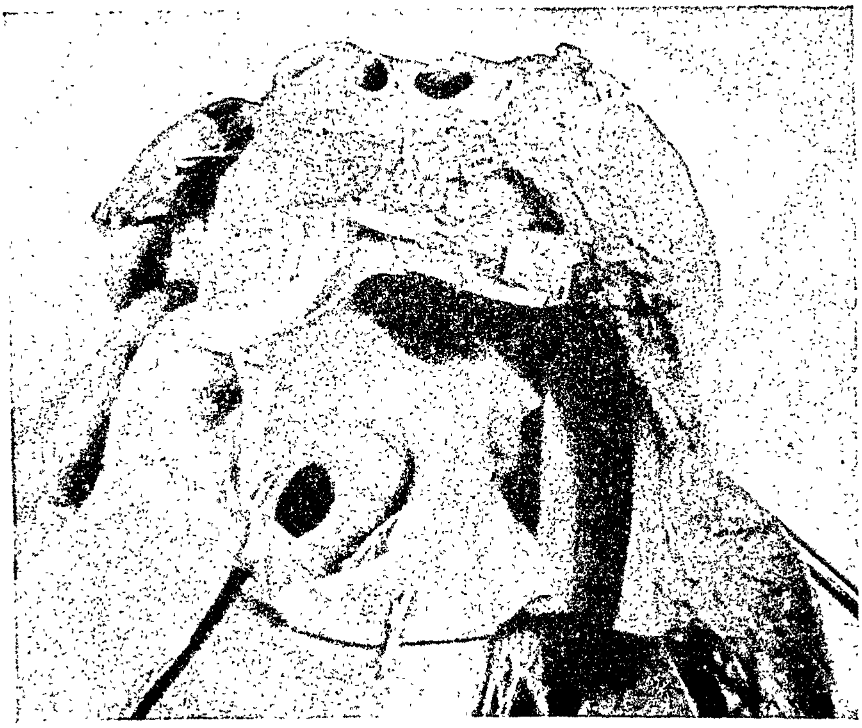

Fig. 2.—Looking toward the pulmonary arterial opening of the defect. Note the cusp of the pulmonary valve running through the opening. This cusp is attached inside the saclike dilatation between the pulmonary artery and the aorta.

COMMENT

This case is of interest because: (1) the patient lived for approximately two years after the communication between the aorta and the pulmonary artery became established; (2) the patient was in the Army in 1917, and presumably no cardiac abnormality was encountered at that time; (3) although the patient had syphilis, no evidence of cardiovascular syphilitic involvement was present; and (4) the correct diagnosis was proposed ante mortem.

In conclusion, the possibility of a communication between the aorta and the pulmonary artery must be considered when the following signs and symptoms present themselves: (1) continuous and severe dyspnea, with signs of pulmonary stasis that are not proportionate to the respiratory embarrassment; (2) signs of right-sided cardiac failure; (3) a loud, continuous, roaring, machine-like murmur, heard best in the aortic area and over the upper portion of the sternum, and associated with a

coarse, continuous thrill throughout the cardiac cycle, best felt at the site of maximal intensity of the murmur; (4) cardiac enlargement, but not aortic in type; (5) electrocardiogram showing no abnormal axis deviation, or a tendency to, or progression toward, right axis deviation; (6) a murmur as described, but no symptoms or signs to fulfill the criteria for establishing a diagnosis of patency of the ductus arteriosus.

SUMMARY AND CONCLUSIONS

1. A case of aortic septal defect, with a communication between the aorta and pulmonary artery, is described.

2. A brief recapitulation of the signs and symptoms of this condition is given.

3. The embryology of the heart is reviewed briefly.

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Abstracts and Reviews

Selected Abstracts

Wiggers, H. C.: Cardiac Output and Total Peripheral Resistance Measurements in Experimental Dogs. Am. J. Physiol. 140: 519, 1944.

The technical procedures for determining cardiac output have been improved by (a) proper adjustment of the concentration and rate of infusion of the NaCl solution so that the salt appeared in sufficient concentration in the femoral blood stream to be easily detected without, at the same time, provoking any abnormality of cardiac action and a consequent artificial change in cardiac output, (b) technical and instrumental improvements for detecting the arrival of the uniform blood-NaCl mixture in a femoral artery, (c) advancements in the technique of withdrawing a sample of the uniform mixture for electroanalysis, and (d) improvement in the accuracy of electrotitration of the control sample to match the blood-NaCl sample.

As a result of the above expedients, the method has been improved to the extent that constantly reproducible measurements of cardiac output were obtained in 145 tests on 42 dogs. Furthermore, statistical analyses revealed that the standard deviation from the mean of these measurements was smaller than any which have been reported for dogs by other investigators. Comparisons of values obtained almost simultaneously by this modified Stewart method and by the more generally accepted Fick method were as comparable as could be expected in both normal and hypotensive dogs.

In 20 dogs, in which arterial blood pressure remained stable, the mean circulatory index, expressed in liters/sq.M./min. was 2.77 and the average of the individual variations was only 0.05. In the remaining 22 dogs, in which arterial pressures fluctuated somewhat (18; S.D. ± 13 mm. Hg) the circulatory index was of the same order of magnitude (2.94), but the average of the individual variations was greater (0.19). There appears, therefore, to be a definite relation between the constancy of consecutive measurements to be expected and the stability of arterial blood pressure.

Although it appears from the results of this and other investigations that the control circulatory index of anesthetized mongrel laboratory dogs generally ranges from 2.5 to 3.3, such values cannot be considered as sufficiently restricted to justify their adoption as controls for any given experiment. On any occasion where it is anticipated that the proposed experimental procedure will modify the cardiac output, it is absolutely essential that several consistent control measurements be obtained. The modified Stewart method excels in its ability to provide quickly such repetitive cardiac output values for consideration by the investigator.

An analysis of these and previously reported data indicates that equivalence in values for the circulatory index in man and dog, or for that matter, among any of the animal species, has not been adequately demonstrated.

The total peripheral resistance of the intact dog under control conditions, concerning which only very meager information has been published, ranged in these dogs from 3,100 to 9,400 A.U. In 105 of 145 measurements, however, it fell within narrower limits (3,600-5,400 A. U.). In certain chronic experiments in which control total peripheral resistance values cannot be obtained prior to the institution of experimental procedures (say states of hypotension or hypertension), the above range for control determinations offers some guide as to the extent to which total peripheral resistance changes may be concerned. Since little correlation was ob-

served between the total peripheral resistance and body surface area, the advantage of introducing surface area into the equation for computing total peripheral resistance seems dubious.

AUTHOR.

Joseph, N. R.: A Direct Current Dielectrograph for Recording the Movements of the Heart. J. Clin. Investigation 23: 25, 1944.

A direct current amplifier for recording capitance changes is described, and its application to the study of cardiac activity is indicated.

It is shown theoretically that, as first approximations, capitance varies directly with the dielectric constant and the volume, and that the potential difference across the condenser plates varies inversely with the capitance.

Records of cardiac activity in human subjects are discussed.

It is pointed out that, due to a large number of complicating factors, the results can be regarded as having only qualitative and empirical significance.

AUTHOR.

Fell, E. H., and Hanselman, R.: Prevention of Shock and Death by Immediate Application of a Pressure Dressing to the Severely Frozen Limbs of Dogs. Ann. Surg. **117**: 686, 1943.

The immediate careful application of pressure dressings (plaster encasement) prevented shock and death of five dogs whose right hind extremity had been severely frozen. The blood volumes, as determined by the hematocrit, were maintained in this group in levels not producing shock.

AUTHORS.

Nathanson, M. H.: Rhythmic Property of the Human Heart. Arch. Int. Med. **72**: 613, 1943.

The clinical importance of the rhythmic property of the heart is emphasized.

Physiologic and pharmacologic studies are reported on the rhythmic function of the human heart, carried out by modifying the cardiac innervation in the following manner: parasympathetic stimulation by pressure on the carotid sinus or administration of mecholyl chloride; and sympathetic stimulation by the administration of epinephrine and related compounds.

Reduction in cardiac rhythmicity by parasympathetic stimulation is more marked in males and in persons of advanced age. A hyperactive vagal inhibition of the heart is frequent in patients having coronary disease.

Studying persons in whom the sinus node can be eliminated for comparatively long periods leads to the conclusion that the rhythmic efficiency of ectopic centers of the human heart is low.

Parasympathetic nerves supply mainly rhythmic foci in the auricles, although the ventricles are influenced in some persons by parasympathetic stimulation. Sympathetic stimulation increases the activity predominantly of ventricular foci.

Digitalis increases reflex vagal inhibition of the heart in many persons. Atropine and quinidine have a vagoparetic action.

In states of depression or absence of the rhythmic function (cardiac or ventricular standstill), the only drugs which effectively increase cardiac rhythmicity are those which stimulate the sympathetic innervation (sympathomimetic amines).

Quinidine and mecholyl chloride tend to suppress the increased ventricular rhythmicity induced by epinephrine.

AUTHOR.

Heimann, H. L., and Shapiro, B. G.: Effects of Plasmoquin, Atebrin, and Quinine on the Electrocardiogram. Brit. Heart J. 5: 131, 1943.

The effects of plasmoquin, atebrin, and quinine on the electrocardiogram of convalescent malarial patients has been investigated.

Plasmoquin increases the amplitude of the various deflections, affecting the T wave most markedly and constantly. In some cases the most striking feature is the effect on the S-T segment which simulates the cardiogram of coronary thrombosis. Whether this is due to an effect on the coronary circulation, the authors are not in a position to state.

Atebrin decreases the amplitude of the various deflections, also affecting the T wave most markedly and constantly. It restores the S-T segment to the isoelectric level after it has been elevated by plasmoquin.

Quinine has an effect similar to atebrin but to a lesser degree.

Differentiation between the effects of plasmoquin on the one hand, and of atebrin and quinine on the other, in a particular patient, may be made on the cardiographic findings given above. Plasmoquin increased the size of the T wave above normal, and quinine and atebrin decreased it below normal. Plasmoquin often has an effect on the S-T segment, as described; this is not seen in the exhibition of either of the other two drugs.

AUTHORS.

Campbell, M.: Latent Heart Block. Brit. Heart J. 5: 163, 1943.

Latent heart block is a convenient term for a conduction time that is prolonged without any dropped beats or higher degree of block.

All those where the P-R interval was above 0.20 second have been included in this series. About 2 per cent of the patients sent to a cardiographic department showed this change, and 141 cases were analyzed. The incidence fell very rapidly from 0.21 to between 0.24 and 0.25 second, and then more slowly to 0.29, after which it was steadier, cases being seen at all levels up to 0.40 second; longer P-R intervals than this were very rare. In nearly half (46 per cent), the P-R interval was not more than 0.22 second. In nearly one-quarter (22 per cent), it was 0.26 second or more.

In addition, 29 cases, which sometimes had dropped beats and sometimes latent block only, and another 27, which sometimes had 2:1 and/or complete heart block and sometimes latent block only, were analyzed.

When there was latent block only, the P-R interval was most commonly between 0.21 and 0.24 second. When latent block interrupted complete and/or 2:1 block, the figure was much the same with a rather wider common range, 0.19 to 0.26 second. On the other hand, when there were at times dropped beats, and at other times latent block only, the P-R interval was, on the average, longer, and was generally from 0.26-0.32 second, possibly because more of these cases were due to a transient acute infection.

As a rule, latent block did not progress to higher grades of heart block. In many it diminished as the effect of an acute infection disappeared; in some it remained at a fairly constant level; and in some it was found, occasionally or from time to time, interrupting complete and/or 2: 1 heart block.

The etiology varied somewhat in the different groups. Where the P-R interval was from 0.20 to 0.25 second, all types of heart disease were represented in much the same proportions as might be found in any collection of cardiac cases.

Where the P-R interval was 0.26 or above, the etiology was more like that found in cases with dropped beats: 41 per cent (as against 11 per cent with a P-R interval from 0.20 to 0.25 second) had acute rheumatism or other active infections, mostly tonsillitis, and there were fewer cases with thyrotoxic or normal hearts.

Cases with latent block and, at other times, 2:1 or complete block were etiologically like the cases with complete heart block, i.e., older patients with atherosclerosis or primary myocardial disease (69 per cent against 26 per cent in the two previous groups, or 86 per cent against 39 per cent if hyperpietic cases were included).

Acute rheumatic carditis was a common cause of P-R intervals that were much prolonged to 0.26 second or above. Chronic rheumatic heart disease occasionally caused these longer values, but was more often responsible for the slighter increases from 0.20 to 0.24 second. Other acute infections sometimes produced quite a long P-R for a time; these included attacks of tonsillitis that were almost certainly not rheumatic.

Latent heart block, especially of the lesser grades, was seen in all types of chronic myocardial disease. Even here it seemed rare for it to progress gradually to complete heart block, though often it interrupted complete or 2:1 block, sometimes after surprisingly long intervals.

Both in thyrotoxicosis and myxedema, long P-R intervals were observed, and this relationship to iodine therapy in thyrotoxicosis needs more investigation.

No instances of latent block due to trauma were included in the series, though such cases have been reported; and one due to blast has been mentioned.

There were no cases where latent block could with certainty be attributed to diphtheria, but such a history was noted in some cases as a possible cause that could not be excluded.

Some curious cases have been described in which P-R intervals, even up to 0.30 second or more, were found without any other evidence of heart disease. As some of these persisted, they did not seem to be due to infection, and it is suggested that exceptional overaction of the vagus may produce unusually long P-R intervals. In some, which have been described rather fully, the longest P-R intervals were irregular or intermittent.

Some few cases with a P-R interval up to 0.22 second or even higher seemed normal in every way.

AUTHOR.

Darrow, C. W., and Pathman, J. H.: Relation of Heart Rate to Slow Waves in the Electroencephalogram During Overventilation. Am. J. Physiol. 140: 583, 1944.

It is demonstrated that, in one-minute periods of overventilation, increase of heart rate tends to be antecedent to, or simultaneous with, slowing of the electroencephalogram. The relation of cardiac and cerebral effects during hypocapnia suggests a possible vagal mechanism. It suggests that reduction of vagal cholinergic vasodilator impulses, at a time when destruction of acetylcholine by cholinesterase is increased by hypocapnia, may be critical. Consequent contractions of the cerebral blood vessels may account for association of cardiac acceleration during overventilation with slow waves in the electroencephalogram.

AUTHORS.

Rich, A. R., and Gregory, J. E.: On the Anaphylactic Nature of Rheumatic Pneumonitis. Bull. Johns Hopkins Hosp. 73: 465, 1943.

In preceding papers the authors have shown that cardiac and arterial lesions having the basic characteristics of those of acute rheumatic fever can be produced experimentally as a result of anaphylactic hypersensitivity. The present comparison of the peculiar lesion of rheumatic pneumonitis with that of the pneumonitis caused by sulfonamide hypersensitivity shows that the two are basically identical, and that both exhibit the primary capillary damage characteristic of focal anaphylactic re-

actions. This provides additional evidence in support of the view that the lesions of acute rheumatic fever may be anaphylactic in origin.

AUTHORS.

Carter, J. B., and Traut, E. F.: Cardiovascular Manifestations in Pernicious Anemia. Arch. Int. Med. 72: 757, 1943.

Cardiovascular manifestations were found in 257 of 300 cases of pernicious anemia. In the presence of severe anemia it is impossible to segregate accurately patients with primary cardiovascular involvement. All of the usual criteria of cardiovascular disease may occur solely as the result of anemia. These symptoms and findings are not restricted to any type of anemia or related to the severity of the anemia. Examination of the blood is essential for dependable differentiation. Cardiovascular manifestations often occur with hematologic decompensation and disappear after treatment or during a remission.

AUTHORS.

Calder, R. M.: The Renal Pathology of Nutritional Hypertension in Rats. J. Exper. Med. 79: 215, 1944.

Rats subsisting on a diet partially deficient in the heat-stable fractions of vitamin B complex are known to experience a rise in blood pressure. The present study shows that after prolonged administration of this dietary, abnormal structural changes occur in the kidneys. The surface of this organ becomes finely granular. The afferent arterioles show degenerative changes, consisting of irregular subendothelial hyaline deposits which encroach on the lumen. The interlobular arteries undergo the same change, plus degeneration of the media; the lumen of these vessels is likewise compromised. Resultant, small, streaklike areas of ischemic atrophy occur in both cortex and medulla, with necrosis of the epithelial lining of the uriniferous tubules. The glomeruli are reduced in size, the number of their component loops decreased, their pattern simplified, and the capillary basement membrane thickened. In addition to these changes, kidneys from animals on a more profoundly deficient diet display numerous areas of hemorrhagic infiltration in the cortical and subscapsular regions.

The possible identity of these lesions with those seen in essential hypertension in man is discussed.

AUTHOR.

Alam, G. M., and Smirk, F. H.: Casual and Basal Blood Pressures. I. In British and Egyptian Men. Brit. Heart J. 5: 152, 1943.

Egyptian men resident in Egypt have much lower blood pressures than British men resident either in Egypt or in England. This difference does not depend upon differences of temperature, diet, or social status.

Half an hour of rest in the sitting posture, together with deliberate emotional desensitization to the presence of the medical examiner and to the procedure of blood pressure measurement, reduced the systolic blood pressure to below 100 in thirteen, and to below 90 in five out of fourteen Egyptian men; to below 105 in thirteen, and to below 100 in six out of twenty-five British men.

Such lowering of the blood pressure was not associated with any symptoms.

AUTHORS.

Alam, G. M., and Smirk, F. H.: Casual and Basal Blood Pressures. II. In Essential Hypertension. Brit. Heart J. 5: 156, 1943.

In essential hypertension considerable differences exist between the casual blood pressure (i.e., as ordinarily measured) and the basal blood pressure. In a group

of 27 patients with essential hypertension, the average casual blood pressure was 195/116 and the average basal pressure was 151/95.

The extent to which the relatively variable casual blood pressure rises above the basal pressure may be termed the supplemental pressure.

The supplemental pressure is that part of the casual blood pressure that represents the response of the cardiovascular system to physical, mental, and emotional stimuli. With rest and habituation to the presence of the observer and his sphygmomanometer, or with sleep, the supplemental pressure falls to, or nearly to, zero.

In Egyptian patients with essential hypertension, both the basal and supplemental pressures are elevated. As an average, one-half of the elevation of the casual blood pressure in these cases of essential hypertension is due to elevation of the supplemental pressure, which is of a removable nature and due to the effect upon a susceptible individual of his physical, mental, and emotional environment.

AUTHORS.

Gatman, M., Amin, M., and Smirk, F. H.: Casual and Basal Blood Pressures. III. In Renal Hypertension. Brit. Heart J. 5: 161, 1943.

The difference between the casual and basal blood pressure is less in renal hypertension than in essential hypertension.

The pressure elevation affects the basal blood pressure more than the supplemental pressure.

It is likely that the blood vessels in renal hypertension are less reactive to vasomotor impulses than they are in essential hypertension.

AUTHORS.

Friedman, M., and Kasanin, J. S.: Hypertension in Only One of Identical Twins: Report of a Case, With Consideration of Psychosomatic Factors. Arch. Int. Med. 72: 767, 1943.

Only one of a pair of identical twins had hypertension and coronary artery disease.

Determinations of renal blood flow and of glomerular filtration were performed on both the normotensive and hypertensive twin. The renal blood flow was found to be similarly reduced in both twins. The glomerular filtration rates also were similar.

Electrocardiograms of the patient showed evidence of myocardial damage, but a tracing made for his brother was normal.

The evidence suggests that psychologic factors may have been of primary significance in the production of hypertension in the affected twin.

AUTHORS.

Mayerson, H. S., Long, C. H., and Giles, E. J.: Venous Pressures in Patients With Varicose Veins. Surgery 14: 519, 1943.

No difference was observed in the height of the venous pressure in "normal" and in varicosed saphenous veins of standing patients. In both types of veins the pressures were usually only slightly higher than the hydrostatic pressure.

The antecubital and saphenous venous pressures of patients with varicose veins were found to be significantly higher than "normal" when the patients were in recumbent position.

These high recumbent venous pressures are believed to be due to an increase in blood volume which enables the individual to compensate for the effects of gravity while standing, but results in an overcompensated state when the recumbent position is assumed.

AUTHORS.

Wilburne, M., and Taylor, H. K.: Multiple Saccular Aneurysms of the Aorta: With Report of Three Cases. Am. J. Roentgenol. 48: 797, 1942.

A review of the literature reveals multiple aneurysms of the aorta to be of relatively infrequent occurrence. However, it is difficult to estimate their frequency with any reasonable degree of accuracy in view of the marked inconsistency of figures in the literature. Further data must be accumulated.

Three cases of multiple saccular aneurysms of the aorta are presented, the principal features of which were the late onset of symptoms, the syphilitic etiology, and the limitation of the lesions to the thoracic aorta. All three patients were males. Necropsies in two cases revealed three aneurysms in the first, and four aneurysms in the second patient. In the third case, roentgen studies (including aortography and kymography) disclosed three aneurysms.

A study of the literature indicates that multiple saccular aneurysms of the aorta are rarely of nonsyphilitic etiology.

AUTHORS.

Watson, J. R., and Miller, R. B.: Arteriovenous Fistula of the Common Femoral Vessels With Extreme Dilatation of the External Iliac Vein: Report of a Case. Surgery 14: 296, 1943.

A case of arteriovenous fistula of the common femoral vessels is reported, in which there was a saccular dilatation of the external iliac vein of sufficient size to produce an abdominal tumor.

A diagnostic sign is described which will permit a clinical differentiation between a venous dilatation and an arterial aneurysm occurring proximal to an arteriovenous fistula.

AUTHORS.

Levy, R. L.: Clinical Types of Coronary Insufficiency and Their Recognition. New York State J. Med. 43: 1836, 1943.

A simple clinical classification of the various types of coronary insufficiency has been presented. It is based upon the concept that this condition occurs when the blood delivered to the myocardium is inadequate, in quanity or quality, for the functional needs of the heart. Ischemia and anoxia are responsible for the symptoms and signs. The most important single decision to be made is whether recent cardiac infarction has occurred. The incidence, time of appearance, and duration of the cardinal signs of infarction have been described. The value of the history, of the electrocardiogram, and of cardiac enlargement have been stressed. By regarding all of the manifestations of disorders of the coronary arteries as expressions of coronary insufficiency, the differentiation of clinical types becomes simplified. Thus logical, and hence more effective, therapeutic procedure is made possible.

AUTHOR.

Schildt, P., Stanton, E., and Beck, C. S.: Communications Between the Coronary Arteries Produced by the Application of Inflammatory Agents to the Surface of the Heart. Ann. Surg. 118: 34, 1943.

The application of asbestos to the surface of the heart brings about the development of new communications between one coronary artery and another.

It reduces the mortality following ligation of a coronary artery.

It reduces the size of the infarct that develops after a coronary artery has been ligated.

The application of asbestos to the surface of the heart is a safe surgical procedure in animals, provided a dosage of about 0.1 to 0.2 Gm. be used rather than larger doses.

Inflammatory agents used on the heart may not be without harmful side effects, and they should not be used indiscriminately.

AUTHORS.

DeBakey, M. E., Schroeder, G. F., and Ochsner, A.: Significance of Phlebography in Phlebothrombosis. J. A. M. A. **123**: 738, 1944.

Phlebography is imperative in all cases of intravenous thrombosis in which the clot is not firmly attached to the vein wall; i.e., in phlebothrombosis.

The procedure is simple, sage, and informative.

Whenever the phlebothrombosis as a defect in the venous system is demonstrated, immediate operation is imperative. This should consist of either ligation of the involved vein above the site of the thrombus or thrombectomy.

Only the prompt recognition of intravenous thrombosis in phlebothrombosis and the institution of measures to prevent the detachment of the clot can decrease the mortality rate from pulmonary embolism.

AUTHORS.

Homans, J.: Pulmonary Embolism Due to Quiet Venous Thromboses and Simulating Cardiac and Pulmonary Disease. New England J. Med. **229**: 309, 1943.

An account has been given of eleven cases of quiet thrombosis in the lower limb causing pulmonary embolism in ambulatory patients. With these cases are discussed six others of similar character, but in which an old thrombophlebitis, an injury, or an illness had preceded the thrombosis.

Consideration of these cases shows that since pulmonary infarction and embolism often simulate cardiac and pulmonary disease, in ambulatory patients otherwise well, they must be considered in the differential diagnosis of many acute and recurrent thoracic disorders.

It may reasonably be concluded from this short series of cases that: repeated embolism, associated with quiet thrombosis, is not rare; the dangerous or fatal quality of any one process is unpredictable; operative treatment, to secure interruption of the thrombosed vein proximal to the source of embolism, is always indicated; conservative treatment, even if not followed by further embolism, is unlikely to prevent continuance or recurrence of the thrombosis; and the use of heparin does not protect against repeated embolism and a fatal outcome.

AUTHOR.

Bartlett, W. M.: Physiologically Induced Myocardial Ischemia as a Test of Circulatory Efficiency as Applied to the Selection of Pilots. J. Aviation Med. **14**: 264, 1943.

The electrocardiographically controlled tilt-table test is of value in the early recognition of coronary inadequacy because positive tests are obtained in 91 per cent of the cases.

This physiologically induced myocardial ischemia will produce objective signs or subjective symptoms in 75 per cent of the cases of heart disease.

The test is of value in differential diagnosis, quickly classifying cases as psychogenic, physiogenic, or organic in origin.

This test will enable the clinician to predict syncope or "blacking-out" and therefore should be used routinely in the selection of flying personnel, whether they are to be trained as pilot, navigator, or bombardier.

Early arterial hypertension by virtue of a stabilized high pulse pressure insures the patient against postural syncope. It may be inferred, therefore, that this type of individual may tolerate dive bombing activities better than a normal person since he is less apt to "black-out" than one with a normal or low pulse pressure.

The tilt-table test will aid in the differential diagnosis between neurocirculatory asthenia, neurasthenia, psychoneurosis, and anxiety state, by objective evidence of myocardial ischemia in the electrocardiogram and/or subjective symptoms.

As a test of circulatory efficiency this test can be utilized in determining the suitability of convalescent soldiers and officers for flying, combat, or limited military service.

AUTHOR.

Collins, D. A., and Hamilton, A. S.: Changes in the Renin-Angiotonin System in Hemorrhagic Shock. Am. J. Physiol. 140: 499, 1944.

Angiotonin (hypertensin) increases in the plasma of dogs subjected to hemorrhage. Renin-substrate (hypertensinogen), often after a preliminary increase, is reduced if the hypotension is of sufficient intensity and duration. Following exhaustion of renin-substrate there is a secondary fall in angiotonin.

AUTHORS.

Neumann, C., Lhamon, W. T., Cohn, A. E., and Galati, C.: A Study of Factors (Emotional) Responsible for Changes in the Pattern of Spontaneous Rhythmic Fluctuations in the Volume of the Vascular Bed of the Finger Tips. J. Clin. Investigation 23: 1, 1944.

Spontaneous variations in the volume of the finger tips are classifiable in three major types and five lesser ones. The three major types are (1) a combination of small alpha waves with large pulse waves (Type 1A); (2) small alpha waves with small pulse waves (Type 1B); and (3) large alpha waves with varying size of pulse waves (Type IIIC).

Individual subjects at rest, free from recognizable external stimuli and not required to carry on intellectual activity, have exhibited changing records. This kind of variability has been found to go closely hand in hand with changes in emotional status. Certain records (Type 1A) were obtained only from subjects in a state fully relaxed and contented. Certain types (Type 1B) occurred when anxiety was dominant. With less anxiety or with elation or resentment, Type IIIC records were obtained. With depression, no uniform alpha-pulse wave pattern was observed. Slight resentment or slight anxiety or a combination of various emotions, none of which was dominant, occurred with intermediate types of records. On the assumption that changes in the degree of activity of the autonomic nervous system parallel changes in emotional status, an explanation is proposed for the changes based on changes in the autonomic nervous system, the results of which have been observed in alpha and in pulse waves, and in combinations of the two.

AUTHORS.

Donovan, M. S., Neuhauser, E. B. D., and Sosman, M. C.: The Roentgen Signs of Patent Ductus: A Summary of 50 Surgically Verified Cases. Am. J. Roentgenol. 50: 293, 1943.

A patent ductus arteriosus can now be safely ligated or completely divided, which places this congenital lesion among the curable forms of heart disease.

The accurate diagnosis of this condition is now vastly more important than formerly, when it was chiefly of academic interest. The roentgenologic signs of patency of the ductus arteriosus have a definite value, although they do not prove the diagnosis, nor does their absence rule it out. In addition, a thorough roentgen study helps the surgeon evaluate the results of operation.

The roentgen findings in 50 cases of patent ductus arteriosus which were verified by operation are presented. These findings in order of frequency are: (a) dilata-

tion of the pulmonary artery; (b) cardiac enlargement; (c) dilatation of the left auricle; (d) engorgement of the intrapulmonary vessels; (e) exaggerated pulsation of the left ventricle and the pulmonary artery (f) ''hilar dance,'' or pulsation of the vessels in the hila of the lungs.

AUTHORS.

Steinberg, M. F., Grishman, A., and Sussman, M. L.: Angiocardiography in Congenital Heart Disease. III. Patent Ductus Arteriosus. Am. J. Roentgenol. **50:** 306, 1943.

Angiocardiography in cases of isolated patent ductus arteriosus reveals:

A distinct localized dilatation of the descending aorta just beyond the isthmus, which varies in size and shape from a localized bulge to a uniformly dilated segment. The appearance may be due either to the infundibulum of the patent ductus or, perhaps, in some cases to a traction aneurysm of the aorta.

An elevation of the main and left pulmonary arteries, the appearance of which suggests that they are drawn toward the isthmus of the aorta.

Moderate to marked dilatation of the pulmonary artery which usually was found. It was absent in 25 per cent of the cases.

Varying degrees of left ventricular dilatation.

In 27 cases of patent ductus arteriosus (12 of which were proved at operation), 26 showed the aortic abnormality described above.

AUTHORS.

Epstein, B. S., and Young, D.: A Correlation Between the Roentgenographic Changes in the Lungs in Left Ventricular Failure and the Circulation Rates. Am. J. Roentgenol. **50:** 316, 1943.

A correlation between prolonged systematic circulation times and roentgenographic changes indicative of pulmonary congestion exists.

Fever or anemia may complicate the differential diagnosis by accelerating an otherwise slow circulation rate in the presence of congestive heart failure. In these instances the roentgenographic findings may be of diagnostic importance.

Patients who have had previous episodes of heart failure may be comfortable and still present both roentgenographic and circulatory time evidences of congestion.

AUTHORS.

Rigler, L. G., and Hallock, P.: Chronic Cor Pulmonale. Am. J. Roentgenol. **50:** 453, 1943.

In the authors' experience right heart enlargement and failure have been a common finding. It is an important cause of death in chronic tuberculosis, in bronchial asthma and other emphysemas, and in silicosis, and is the usual cause of death in pulmonary arteriosclerosis. Every case of chronic lung disease should be examined with this in mind. By roentgenoscopic and roentgenographic study in all positions, the characteristic enlargement of the pulmonary artery and the right ventricle may be demonstrated. The roentgen findings are by far the most important means of establishing the presence of right heart enlargement before failure has supervened and are most helpful in the differential diagnosis.

AUTHORS.

Sosman, M. C.: The Technique for Locating and Identifying Pericardial and Intracardiac Calcifications. Am. J. Roentgenol. **50:** 461, 1943.

This article sums up the technical procedures and adds a few details which have improved the accuracy of demonstration of calcified areas in the heart on roentgen examination. The author believes that roentgenoscopy is the much more important

part of the examination. Roentgenograms rarely add anything if the roentgenoscopy is carefully and thoroughly done. The roentgen kymogram has been of very little help. Oblique roentgenograms of the heart, both right and left, are of more value than lateral views and should be part of every record.

McCulloch.

Leach, J. E.: Effect of Roentgen Therapy on the Heart: A Clinical Study. Arch. Int. Med. 72: 715, 1943.

From a study of 84 patients with various types of neoplasms and one with tuberculosis of mediastinal lymph nodes, who were carefully observed to determine the effect of roentgen therapy on the heart, there is no evidence that the heart is affected by roentgen radiation as used at present.

The depression of the blood pressure during and after roentgen therapy is probably due to (1) insufficient nourishment, (2) anemia, (3) fever, (4) neoplastic toxemia, (5) general radiation effect, and (6) possibly absorption of split protein products.

A carotid sinus syndrome may be induced by cervical metastatic disease and will respond to the usual therapy.

Adhesive or constrictive pericarditis may occur following severe radiation pleuropulmonitis complicated by infection.

Cardiac arrhythmia, when present, may be expected to respond to the usual therapy.

A sequence of changes is observed in electrocardiograms made before, during, and after, roentgen therapy.

Author.

Spiegel, R., Friedlander, M., and Silbert, S.: Prevention of Gangrene Following Ligation of Major Arteries—Experimental Study. Surg., Gynec. & Obst. 77: 162, 1943.

Bilateral ischemic paralysis and gangrene of the lower extremities in cats was produced in ten of twelve experiments in which the three terminal branches of the abdominal aorta and the anastomotic branches of the femoral arteries were ligated.

Unilateral ischemic paralysis and gangrene of the lower extremity was produced in cats in four of five experiments in which the middle hemorrhoidal, the common iliac, and the homolateral anastomotic branches of the femoral artery were ligated.

In three of six experiments on dogs, gangrene of the lower extremities was produced by ligating the three terminal branches of the aorta.

The blood supply to the lower extremity after ligation of the common iliac artery, was maintained for several hours by autotransfusion. In some experiments the blood was transfused from donor arteries. In other experiments blood was aspirated from the abdominal venous reservoir and pumped into the femoral artery by a pipetting machine.

Authors.

Pemberton, J. de J., and Black, B. M.: Surgical Treatment of Acquired Aneurysm and Arteriovenous Fistula of Peripheral Vessels: Review of Sixty-Seven Cases. Surg., Gynec. & Obst. 77: 462, 1943.

From a review of the records of 67 patients who suffered from acquired, peripheral aneurysm and arteriovenous fistula, and who were treated by operation at the clinic, it would seem that the exact diagnosis can be made usually before operation, and that a correct evaluation of the status of the collateral circulation is possible by means of clinical tests before operation and by noting the amount of retrograde

bleeding from the principal artery at the time of operation (Henle-Coenen test). In cases of arterial aneurysm of the leg in which there is doubtful collateral circulation, much improvement can be expected to follow lumbar sympathectomy, and postoperative vasospasm is also prevented. Endoaneurysmorrhaphy with or without extrasaccular ligation of the principal artery, and proximal and distal ligation of the artery and excision of the sac are the procedures of choice for the treatment of aneurysms of peripheral arteries. In the case of peripheral arteriovenous fistula, the procedure of choice for the radical cure of the condition is, clearly, quadruple ligation and excision. Another satisfactory but less certain procedure is quadruple ligation and obliteration and, occasionally, simple ligation of the communication betweeen artery and vein may be carried out.

AUTHORS.

Lawrence, J. S., and Allott, E. N.: Heart Changes in Alkalosis. Brit. Heart J. 5: 128, 1943.

The cardiographic findings in a severe case of alkalosis are described.

Marked prolongation of systole was present, so that systole came to be greater than diastole. This was associated with an alteration in the relationship of the heart sounds and impaired cardiac function.

The similarity to changes found in hypocalcemia is discussed.

AUTHORS.

Wilburne, M., and McGoldrick, T. A.: Prolonged Administration of Sulfapyridine in Subacute Bacterial Endocarditis: Report of Case Following Administration of 621 Grams. *Ann. Int. Med.* 17: 333, 1942.

The authors have presented a case in which 621 grams of sulfapyridine were administered over a period of eight months. No untoward effects were observed except for the occurrence of mild nausea and vomiting during the first month. At necropsy the organs reveals no characteristic changes attributable to sulfapyridine. The literature contains no previously reported case of the administration of so large a dosage of sulfapyridine with the absence of clinical and post-mortem evidence of toxicity. The case is of interest in view of the frequency with which toxic reactions appear when the usual therapeutic dosages are employed.

AUTHORS.

Bruger, M., Wright, I. S., and Wiland, J.: Experimental Atherosclerosis. V. Effect of Testosterone Propionate and Estradiol Dipropionate on the Cholesterol Content of the Blood and the Aorta in Castrate Female Rabbits. Arch. Path. 36: 612, 1943.

Castration per se does not alter the cholesterol content of the blood or that of the aorta in young female rabbits.

Testosterone propionate and estradiol dipropionate administered at frequent intervals over a period of one hundred days fail to influence the cholesterol content of the blood or that of the aorta in female castrates.

Feeding cholesterol produces hypercholesteremia and increased deposition of cholesterol in the aorta, regardless of the presence or the absence of the female gonads.

Testosterone propionate and estradiol dipropionate inhibit the hypercholesteremia and prevent the excess deposition of cholesterol in the aorta of the female rabbit fed cholesterol, but when the gonads are removed this protective action is abolished.

AUTHORS.

Raab, W.: Sudden Death of a Young Athlete With an Excessive Concentration of Epinephrine-Like Substances in the Heart Muscle. Arch. Path. 36: 388, 1943.

In the case of death of a young, seemingly healthy athlete the only striking pathologic change observed at autopsy was an excessively high concentration of epinephrine-like substances in the heart muscle (the highest of all values observed in a series of 54 normal and pathologic human hearts).

From the results of studies of the hearts of animals and man it is concluded that this excessive concentration of sympathomimetic amines was incompatible with survival and was the immediate cause of death.

Chemical examination of the heart muscle may prove to be of forensic usefulness in cases of unexplained sudden death, particularly in those of death occurring under emotional or physical strain.

AUTHOR.

Coburn, A. F.: Salicylate Therapy in Rheumatic Fever: A Rational Technique. Bull. Johns Hopkins Hosp. 73: 435, 1943.

A simple method for the determination of the salicyl radicle in oxalated blood is described.

Data on plasma salicylate levels in relation to dosage of sodium salicylate administered to rheumatic fever patients are presented.

Observations on the relation of rheumatic activity to the plasma salicylate level show that twenty patients maintained at 359 to 400 gamma per cubic centimeter manifested a prompt and progressive subsidence of rheumatic inflammation, and that twenty other patients with plasma levels below 250 gamma per cubic centimeter continued to manifest an active inflammatory process.

It is pointed out that the intravenous administration of sodium salicylate is required to obtain a rapid rise in the plasma concentration of salicylate to 400 gamma per cubic centimeter.

A therapeutic technique for the use, first of intravenous and later of oral salicylate, is suggested for the rapid development and maintenance of plasma salicylate levels above 350 gamma.

The results of two years' experience with this technique show that none of 38 rheumatic patients treated with 10 grams of sodium salicylate, daily, developed valvular heart disease, and that 21 out of 63 similar cases who received only small doses of sodium salicylate developed physical signs of heart disease.

The observations suggest that a plasma salicylate level of at least 350 gamma per cubic centimeter may be required to suppress the rheumatic reaction, and that plasma levels below 200 gamma per cubic centimeter may be sufficient to relieve symptoms while masking a progressive inflammatory process.

AUTHOR.

Middleton, S., and Wiggers, C. J.: Some Effects of Pectin Solutions During Posthemorrhagic Hypotension. Am. J. Physiol. 140: 326, 1943.

A 1.5 per cent buffered pectin solution exerting an oncotic pressure of 67 to 68.7 cm. of water was injected at a rate of 3 to 5 c.c. per minute after varying periods of posthemorrhagic hypotension (50 mm. Hg).

The usefulness of such solutions is apparently limited to the early periods of such hypotension. Given after thirty minutes, 11 out of 19 dogs showed a satisfactory hemodynamic response for four to six hours after administration.

Pectin infusions, given after a posthemorrhagic dilution of blood has already occurred, cause a further dilution by virtue of the fluid injected, and this is rather

well maintained for four to six hours. Evidence that additional dilution results from osmotic attraction of water from tissues was not found.

No correlation existed between maintenance of hemodilution and favorable hemodynamic reactions; on the contrary, the animals that recovered usually showed some tendency to reconcentration. This suggests that the demonstrated ability of a colloid *a* to maintain an effective oncotic pressure over a considerable time interval, and *b*, to increase blood volume in normal animals is not a satisfactory criterion of its *physiologic* usefulness.

While no evidence was obtained experimentally or at necropsy that the rapid sedimentation and agglutination produced by such solutions is harmful, the occurrence of a precipitate failure of the circulation in too many experiments, and the inability to overcome this by subsequent large infusions of blood suggest that pectin infusions may exert some deleterious influence when used after severe hemorrhage. Consequently, caution should be exercised in the employment of pectin solutions in such conditions.

These conclusions do not necessarily apply to states of hypotension produced otherwise than by loss of blood, and, particularly, when hemoconcentration exists.

AUTHORS.

Nicholson, J. H.: The Intravenous Use of Lanatoside C. New England J. Med. **229:** 619, 1943.

Intravenous digitalis therapy may be necessary when rapidity of action is desired and when the patient is unable to take medication by mouth owing to nausea and vomiting or to unconsciousness. Lanatoside C (cedilanid) given intravenously has a wide margin of safety, requires no fractional dosage, and is rapid in action. It appears to have a definite advantage over the glycosides of *Digitalis purpurea.*

AUTHOR.

Notice

Dr. Barnett Binkowitz, of Brooklyn, New York, has called our attention to the fact that, in 1933, in the *Medical Journal and Record,* volume 137, page 426, he published an article entitled "An Early Sign of Cardiac Decompensation," in which he reported the observations as those described by Dr. A. M. May in his paper on "The Tongue Sign for High Venous Pressure," which appeared in the November, 1943, issue of the AMERICAN HEART JOURNAL (volume 26, page 685).

We feel sure that Dr. May must not have known about Dr. Binkowitz' report, and, therefore, that no question of plagiarism is involved. Nevertheless, we regret the fact that Dr. Binkowitz' previous work was overlooked.

The Editors.

Book Review

Doenças do Coração (Patologia e Terapêutica): By Dr. Reinaldo Chiaverini, Docente livre de Clinica Médica da Faculdade de Medicina da Universidade de São Paulo. Edições Técnicas Brasileiras Ltda., São Paulo, 1943, 672 pages, 73 illustrations.

This book on cardiology is undoubtedly out of the ordinary. Emphasis is placed on the cause and treatment of heart disease, with a fair description of the pathologic changes. Description and discussion of the clinical phenomena are, on the other hand, purposely avoided. Although some mention is made of signs and symptoms in reference to diagnosis, it is difficult to see how students of medicine will be able to obtain a complete picture of disorders and diseases of the heart from this book.

The classification of heart disease follows Cabot's outline. A short chapter of nine pages is devoted to congenital heart disease. In the next chapter the author describes ''cardio-articular rheumatism'' without clearly differentiating between active stage and effects of the disease. Much space is devoted to treatment of this so-called cardio-articular rheumatism by means of salicylates, sulfonamides, and aminopyrine. Inasmuch as no clear description or evaluation of the various valvular defects is given, one wonders whether the reader will treat a patient with mitral stenosis only with these drugs.

The succeeding chapters deal with cardiovascular syphilis, bacterial endocarditis, acute and chronic infectious diseases, hypertensive heart disease, coronary heart disease, cor pulmonale, endocrine diseases, beriberi, anemias, pregnancy, pericarditis, cardiac trauma, and neurocirculatory asthenia.

Functional disorders are grouped in the second part of the book. Four separate chapters are devoted to disorders of the cardiac rhythm. Angina pectoris and congestive failure are followed by a plethoric chapter (over 100 pages) on treatment of congestive failure. The last chapter of the book describes failure of the peripheral circulation.

The chapters are peculiarly arranged. For example, bacterial endocarditis is widely separated from rheumatic endocarditis, and coronary arteriosclerosis and angina pectoris are separated by 240 pages dealing with other subjects. Neurocirculatory asthenia is included among ''etiologic types of heart disease,'' and shock, among ''cardiovascular dysfunctions.''

A possible explanation is the acknowledged purpose of disengaging from anatomic lesions in order to link heart disease with the entire category of diseases that may affect the rest of the body. This reviewer confesses his inability to see that the purpose was successfully accomplished.

The best chapter in the book is Chapter VI, in which heart disease in acute and chronic infections is described.

The figures are few and often poor.

Dr. Paul D. White contributes an excellent foreword on methods of approach to the fundamental concepts of heart disease.

Aldo Luisada.

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The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

*Executive Committee.

American Heart Journal

VOL. 27 | JUNE, 1944 | No. 6

Original Communications

THE DISTRIBUTION OF POTENTIAL OF VENTRICULAR ORIGIN BELOW THE DIAPHRAGM AND IN THE ESOPHAGUS

JOHN D. HELM, JR., M.D., GRACE H. HELM, A.B., BOSTON, MASS., AND CHARLES C. WOLFERTH, M.D., PHILADELPHIA, PA.

RECENT studies of Wolferth, Livezey, and Wood,[1,2] using methods by which the potential transmitted to an exploring electrode can be reflected in electrocardiograms with minimal distortion, have shown that a pattern of potential variation which they called the diaphragmatic pattern is widely distributed over the surface of the human body below the level of the diaphragm. A few observations made with an exploring electrode in the stomach and in the esophagus below the auricular level indicated that the diaphragmatic pattern tends to be distributed to these areas, also. Limited animal experiments in the dog and rat, in which the exploring electrode was paired with one inserted in the right foreleg, likewise indicated that one pattern of potential is distributed to the legs, the surface of the trunk below the diaphragm, and the abdominal cavity, including the undersurface of the diaphragm except the part very near the heart.

In connection with a study by Forster, Helm, and Ingelfinger[3] on action potentials of the gastrointestinal musculature, it was decided to make further observations on the comparison of ventricular patterns of potential variation developed on the left leg with those of the front and back of the trunk below the level of the umbilicus,* the small

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Aided in part by a grant from the E. H. Brewer Co., Inc., Worcester, Mass.

Received for publication Nov. 6, 1943.

*The studies of Wolferth, Livezey, and Wood[2] have indicated that the patterns of potential variation recorded at various positions on the body surface between the levels of the parietal attachments of the diaphragm and the umbilicus are composites made up of the diaphragmatic pattern, and patterns better recorded above the diaphragm. The decrement in the latter is so rapid below the diaphragm that they usually exert a negligible influence on potential patterns below the level of the umbilicus. These composite effects, however, between the levels of the diaphragm and the umbilicus, make this zone of dubious value for the study of ventricular potential. For this reason it was not included in the present study.

intestine, duodenum, stomach, and esophagus. Such observations, it seemed to us, should yield information regarding the distribution of the diaphragmatic pattern of potential and also throw some light on the usefulness of inserting electrodes into the gastrointestinal tract for study of the cardiac action currents.

MATERIAL AND METHODS

The subjects were patients from the Gastrointestinal Clinic and the Medical and Surgical Wards of the Massachusetts Memorial Hospital. Electrocardiograms were made with a Sanborn tri-beam galvanometer. In the experiments in which the exploring electrode was placed in the gastrointestinal tract, three types of electrodes were used: (1) a solder disc electrode 4 mm. in diameter on a tube described previously,[3] (2) a standard Rehfuss tip 9 by 17 mm., or (3) a small metal tip 5 by 7 mm. The tips were soldered to No. 32 enameled copper wire, conducted through rubber tubing so that insulation was complete except for the tip. The tubes were passed either orally or through the nose, and were manipulated into the desired position under fluoroscopic guidance. With the exception of four cases mentioned, the exploring electrode was paired with one placed over the spine of the right scapula, an area shown by the method of balanced potentials to be one of relatively slight cardiac potential variation.[2]

COMPARISON OF VENTRICULAR PATTERNS OBTAINED WITH THE EXPLORING ELECTRODE ON THE LEFT LEG AND VARIOUS OTHER POSITIONS

Anterior Abdominal Wall.—The pattern of potential variation found with an exploring electrode on the anterior abdominal surface midway between the umbilicus and the symphysis was compared with the left leg pattern in 18 cases (Fig. 1, *A*, *B*, *C*, *D*, and *E*). In 14 cases the patterns were practically identical in every respect, including amplitude of deflections. In three cases the patterns were practically the same qualitatively, but the amplitude of deflections recorded from the abdominal wall was slightly smaller than that recorded on the left leg. In one case the patterns differed slightly in that an S deflection (new nomenclature) extended a little further below the isoelectric line in the abdominal pattern.

Posterior Abdominal Wall.—The potential patterns recorded with an exploring electrode on the midline of the back below the umbilical level were compared with the potential patterns of the left leg in the same 18 cases (Fig. 1, *A*, *B*, *C*, *D*, and *E*). In all cases the patterns were similar qualitatively, but in only two were the deflections of approximately the same size. In the other 16 cases the deflections were smaller when the exploring electrode was placed over the back than when it was placed on the leg.

Small Intestine.—A comparison of the potential variations of the interior of the small intestine beyond the duodenum with those of the left leg was made in four cases (Fig. 2, *A*, *B*, and *C*). In these cases, the exploring electrode, which was passed beyond the ligament of

Treitz, was paired with an electrode on the right arm, and this lead compared with Lead II. In each of the four cases the two leads were practically identical. In two of the cases in which the electrode in the intestine was paired with one on the left leg, only a negligible difference of potential was recorded.

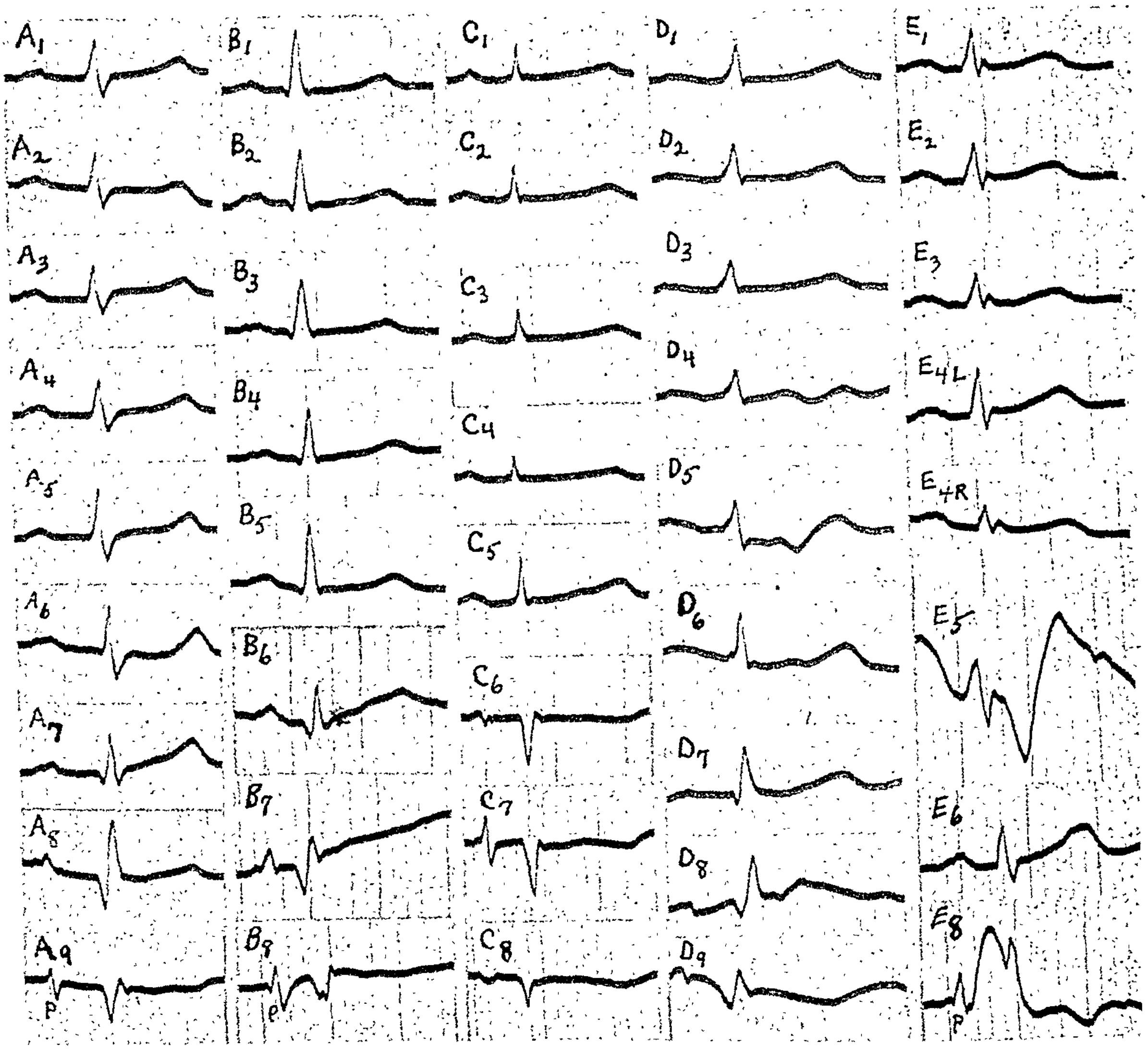

Fig. 1.—The letters *A*, *B*, *C*, *D*, and *E* designate cases, and the numerical subscripts, the positions of the exploring electrode. Thus, *1* designates the left leg; *2*, the anterior abdominal wall below the umbilicus; *3*, the mid-back at the same level as *2*; *4*, the duodenum (*4 R* the right side and *4 L* the left side); *5*, the stomach; *6*, just within the lower end of the esophagus; *7*, approximately 1 to 1½ inches higher in the esophagus; *8*, at the mid-cardiac level; and *9*, the level of the top of the heart.

In *A* note the similarity of pattern with the exploring electrode at various positions from the left leg to the lower end of the esophagus, and then, as the electrode is moved to positions higher in the esophagus, the gradual development of a large Q deflection and inversion of the T wave (the "endocardial pattern"). In *B* the similarity of pattern is preserved as near the heart as the stomach. At the lower end of the esophagus, the beginning change to the endocardial pattern is reflected by an increase in amplitude of the Q wave. In *C* the pattern is also preserved as near to the heart as the stomach, but at the lower end of the esophagus the pattern is already of the endocardial type. In *D*, a case in which there was marked enlargement of the liver and spleen, the QRS complex pattern is preserved as high as the lower end of the esophagus, but there is RS-T segment deflection in the duodenal, stomach, and lower esophageal leads; this is, in all probability, an artifact caused by movement of the electrode. In *E* the correspondence between the QRS complex of the lead with the exploring electrode on the leg and the two leads made with the exploring electrode in different parts of the duodenum is the poorest obtained between leg and duodenal leads. In the lead made with the exploring electrode in the stomach (E_5), note the marked distortion following the QRS complex, and, in the esophageal lead (E_8), the marked distortion following auricular activation. These effects, like those pointed out in *D*, are regarded as artifacts produced by movement of the electrode. They recur regularly with every beat.

Duodenum.—The potential patterns recorded with an exploring electrode in the descending portion of the duodenum were compared with those of the left leg in 24 cases (Fig. 1, *A*, *B*, *C*, *D*, and *E*). In 14 cases the patterns were practically identical. In 5 cases the patterns were the same except that the deflections in the duodenal lead were uniformly smaller (Fig. 1, *C*). In one case the patterns were the same except that the deflections in the duodenal lead were uniformly larger. Of the other four cases, three showed minor differences in the QRS complex from that of the corresponding leg lead, and two showed differences in T waves. In one of these four cases in which leads were made from both the descending and distal portions of the duodenum, leads from neither portion showed accurate correspondence with the leg lead with respect to the S deflection (Fig. 1, *E*). Inspection of these tracings, however, suggested that the mean potential of the two duodenal areas would have resembled the leg pattern of potential variation fairly closely.

Stomach.—The patterns of potential variation of the left leg were compared with those of one or two parts of the stomach in 36 cases.

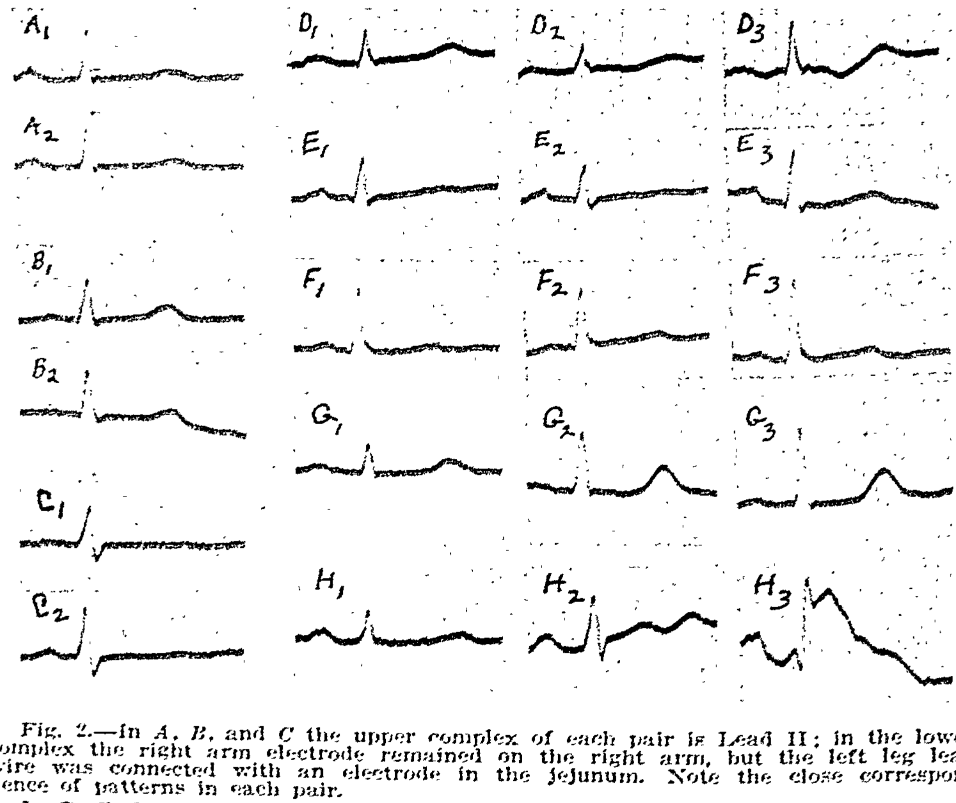

Fig. 2.—In *A*, *B*, and *C* the upper complex of each pair is Lead II; in the lower complex the right arm electrode remained on the right arm, but the left leg lead wire was connected with an electrode in the jejunum. Note the close correspondence of patterns in each pair.

In *D*, *E*, *F*, and *G* the subscript *1* designates a lead with the exploring electrode on the left leg, paired with an electrode over the spine of the right scapula. The subscript *2* designates that the exploring electrode was in the right side of the stomach, and *3*, that it was in the left side of the stomach. Note that the deflections were larger when the exploring electrode was in the left side of the stomach. In *D* and *E* minor differences of patterns are found in the QRS complex, but in *F* and *G* there is close correspondence of the entire ventricular patterns except for the amplitude of deflections.

In H_1 the exploring electrode was on the left leg in H_2 in the stomach and, in H_3 in the lower end of the esophagus. Note the marked RS-T segment deflection in the esophageal lead, which is almost certainly an artifact produced by movement of the electrode during the heartbeat. The diphasic T wave in D_2 and D_3 was probably caused by the same phenomenon.

We wish first to present the data in 12 cases in which the tracings were made with the exploring electrode in the pyloric region, and then on the left side in the fundus as near the left side of the diaphragm as possible. In six of these cases the potential pattern of the pyloric region was similar to that of the left leg (Fig. 2, *F*). In three other cases the patterns were qualitatively similar, but the deflections were larger in two (Fig. 2, *G*) and smaller in one. In the other three cases there were minor changes of the QRS pattern in two and slight distortion of the T wave in one (Fig. 2, *D*).

When the exploring electrode was moved to the left side under fluoroscopic guidance, in 10 of these 12 cases the pattern of the QRS complex remained qualitatively the same as in the pyloric region. In nine the deflections were definitely larger (Fig. 2, *F* and *G*), but in one case they were of the same size. In the other two cases the S deflection extended slightly lower, but otherwise the QRS complexes were similar. The T wave was of the same shape in 10 of the 12 cases at the two positions. When the QRS deflections were of greater amplitude, the T wave was also of greater amplitude. In two of the cases in which the QRS complexes were similar, the T wave was somewhat diphasic in tracings made with the electrode situated to the left, whereas it had been a simple upright curve in the lead with the electrode in the pyloric region in one case, and slightly diphasic in the other (Fig. 2, *D*).

In the remaining 24 cases, in which no attempt was made to place the electrode in any particular part of the stomach, but in most of which it lay somewhat to the left, the results were as follows: In three cases the pattern was practically identical with that of the left leg (Fig. 1, *B*). In 12 additional cases the pattern was practically the same qualitatively as that of the left leg, but all the deflections were greater in amplitude (Fig. 1, *A* and *C*). Among the nine cases in which the pattern was classified as different from that of the leg, the QRS complex was similar in five cases, showed minor differences in three (Fig. 1, *D*), and a lack of resemblance in one case only (Fig. 1, *E*). In two of the nine cases, the T wave was similar to that of the leg leads, in five the T wave was diphasic, with the inverted phase first (Fig. 1, *D*), and in two cases there was marked distortion, with RS-T segment deflection (Fig. 1, *E*).

Esophagus.—Studies of esophageal patterns of potential were made in 30 cases. Tracings were made with the exploring electrode at four esophageal positions. The first position was as low as possible. When this could not be ascertained with certainty by fluoroscopic inspection and resistance to pull on the electrode, small amounts of barium sulfate suspension were injected through the tube, so that the tip could be placed in the terminal half-inch of the esophagus. The second position for the exploring electrode was approximately 1 to 1½ inches orad from the first. The third position was at a level about midway between the top and bottom of the heart. The fourth position was level with the top of the auricular shadow. In the first 11 cases the Rehfuss

tip, with its length of 15 mm., was used. In the last 19 cases the tip with the length of 7 mm. was used.

The patterns of ventricular potential variation recorded with the exploring electrode at the third and fourth positions were entirely different from that of the left leg in every case (Fig. 1, *A, B, C, D,* and *E*). The QRS complex was invariably initiated by a large Q wave; in some cases the potential remained negative throughout the entire QRS complex (Fig. 1, *C*), but in others there was a rise above the base line in the latter part (Fig. 1, *A* and *B*). The T wave was either inverted or practically isoelectric in all cases (Fig. 1, *A, B, C, D*, and *E*).

The lower esophageal pattern was practically the same as that of the left leg in two of the cases in which the larger electrode, and six of those in which the smaller electrode, was used, except that the deflections in the esophageal lead were larger (Fig. 1, *A*). In two cases in which the larger electrode, and 10 in which the smaller electrode, was used, there were only minor differences in the QRS or T deflections, or both, from the potential pattern of the left leg (Fig. 1, *D*). In two cases in which the large tip electrode was used, the lower esophageal pattern resembled that obtained at the auricular level (Fig. 1, *C*), and in four the pattern seemed intermediate in type between those recorded with the electrode in the stomach and at the auricular level of the esophagus (Fig. 1, *B*). In these cases the QRS complex was initiated by a Q deflection of considerable amplitude. When the small electrode was placed in the lower part of the esophagus, none of the patterns were the same as those obtained at the auricular level, and, in only two cases, were the tracings intermediate in form between those recorded from the stomach and from the auricular level of the esophagus. In one case in which the larger, and one in which the smaller, electrode was used, the lower esophageal patterns were quite different from those obtained from the left leg, or stomach, and also from those obtained at the auricular level (Fig. 1, *E*). The patterns recorded with the exploring electrode 1 to 1½ inches orad from the lowest part of the esophagus had the following characteristics: When the pattern obtained from the lower esophagus resembled that of the auricular level, the pattern of this position was also similar (Fig. 1, *C*). When the pattern of the lower esophageal level was intermediate in type between the stomach pattern and that of the esophagus at the auricular level, the pattern 1 to 1½ inches orad from the lower portion showed more of the Q deflection. Even when the pattern of the lower esophagus (Fig. 1, *B*) resembled that of the left leg, the pattern 1 to 1½ inches orad showed some of the Q deflection more fully developed at higher levels (Fig. 1, *A*).

DISCUSSION

The data presented above indicate that there is remarkable uniformity in the patterns of potential variation distributed to the left leg, both the anterior and posterior surfaces of the trunk below the level

of the umbilicus,* and the small intestine, including the duodenum. There is no appreciable tendency toward decrement in this pattern of potential variations between a position so near the heart as the descending portion of the duodenum and so far away as the left leg. However, it is of interest that a distinct tendency toward decrement is found on the surface of the back in positions considerably nearer the heart than the left leg.

The correspondence between the patterns obtained with an exploring electrode in the stomach and those recorded with an electrode on the left leg, although remarkably close, particularly in so far as the QRS complex is concerned, is nevertheless not as exact as in the case of the positions discussed above. Wolferth, Livezey, and Wood[2] have pointed out that the preservation of patterns of potential variation throughout extensive regions of the body does not apply to regions very near some part of the external surface of the heart. It had, of course, long been known that tracings made with an exploring electrode on various precordial areas revealed differences in the potential patterns of areas near each other. However, it was also shown that the patterns obtained in experimental animals from positions within the lungs near the heart and near each other differed, and those obtained from positions on the diaphragm near the heart and near each other also differed. Moreover, these patterns obtained from the lower surface of the diaphragm near the heart varied somewhat from the pattern recorded from all other parts of the undersurface of the diaphragm.

In some of the cases studied in this series it was noted fluoroscopically that the exploring electrode was near that part of the diaphragm directly underlying the heart. It was in such cases that the correspondence of the stomach and leg patterns of potential variation was less exact, although even under these circumstances there was usually a fairly close resemblance. In the series of cases in which tracings were made from two stomach positions, the effect of decrement in potential variations as distance from the heart increased was clearly demonstrated. However, in some cases there seemed to be no further decrement between the pyloric region and the left leg.

The distortion of the T wave and the RS-T segment in a few of the electrocardiograms made with an exploring electrode in the stomach and the lower end of the esophagus perplexed us somewhat. It seemed most likely that these changes resulted from adventitious causes. There was no correlation with the level of gastric acidity, and no other reason to believe that there were polarization effects. Because these changes were more likely to be found when the electrode was known to be near the heart, we attributed them to movement of the electrode

*Unpublished studies (Wolferth, C. C., and Livezey, M. M.) made in cases of intraventricular conduction defect and bundle branch block, with their more intricate patterns, confirm the general conclusions derived from this study regarding the distribution of potential on the trunk below the level of the umbilicus, but show that the correlation between patterns on these areas and the left leg is not quite as close as is suggested by studies on normals. In general, the potential variations on the left flank tend to be slightly greater in amplitude than those of the anterior or posterior surfaces of the trunk or the left leg, and those of the right flank are less than those of the other positions.

caused by the heartbeat. This view receives some support from the fact that at, and slightly below, the auricular level in the esophagus, marked deviation from the isoelectric line is sometimes observed just after the "QRS group" of auricular deflections recorded at that level. The fact that such artifacts may occur obviously impairs the value of stomach and esophageal electrocardiograms.

The esophageal electrocardiograms made with an exploring electrode at or slightly below the auricular level bear a resemblance in their general characteristics to those obtained in experimental animals, with an exploring electrode within one or the other ventricular cavity. We are in agreement with the suggestion of Brown,[4] to the effect that, at the auricular level, endocardial potential is tapped by the exploring electrode. At positions between this level and the lower end of the esophagus the effect of this pattern was clearly discernible, in that a Q deflection of considerable magnitude was usually present. At the lower end of the esophagus the pattern found in nearly all cases was one of three types, namely, (1) the diaphragmatic pattern, (2) the "endocardial" pattern similar to that recorded at the auricular level, or (3) a composite pattern intermediate in type between the diaphragmatic and endocardial patterns. Our limited studies suggest that the chance of recording the diaphragmatic pattern of potential in the lower portion of the esophagus is greater when a short electrode is used, but, even with a very small electrode, the endocardial pattern may be recorded from that region.

Consequently, entirely aside from the possibility of artifact in esophageal electrocardiograms, the variability in the types of curves obtained in normals from the lowest part of the esophagus has made us feel that standardization of leads in this area, to the extent that reliable opinions can be formed regarding interpretation, will prove to be extremely difficult, if it can be accomplished at all. Moreover, at present there is very little reason to think that any great advantage is obtained by recording the diaphragmatic pattern in the esophagus in addition to that of the surface of the leg. However, the endocardial pattern recorded at the auricular level cannot be obtained with an exploring electrode on the body surface. Further investigation will be required, particularly in patients with various types of cardiac damage, before a decision can be reached as to whether study of the esophageal pattern at the auricular level has any clinical value aside from study of auricular activity. If not, there will be little reason to think that electrical exploration of the digestive tube adds anything of value to study of the ventricles, over and above what can be learned by placing electrodes on more readily accessible parts of the body.

SUMMARY

1. The pattern of ventricular potential variation distributed to the left leg, which Wolferth, Livezey, and Wood called the diaphragmatic

pattern, is likewise distributed to the anterior and posterior surfaces of the abdomen below the umbilicus, and to the jejunum and the duodenum. It is distributed to the stomach, although, in certain cases, particularly when the exploring electrode is moved to a position directly under and near the heart, the pattern is not faithfully maintained.

2. The amplitude of potential variations does not tend to change materially between a position as near the heart as the pyloric region of the stomach and as far away as the left leg. Decrement between the heart and the posterior surface of the back, however, tends to be greater than that between the heart and the left leg. There is appreciable decrement between the fundus and the pyloric end of the stomach.

3. The pattern of ventricular potential variations recorded with the exploring electrode in the esophagus at the auricular level is similar in its general characteristics to the pattern obtained when an exploring electrode is placed within a ventricular cavity. When an exploring electrode is placed at the lower end of the esophagus, the pattern recorded may resemble either the pattern with widespread distribution below the diaphragm or the "endocardial pattern" recorded at the auricular level, or it may be intermediate in form between these two.

4. When an electrode is placed either in the stomach or esophagus in positions close to the heart, bizarre electrocardiograms are occasionally obtained. These bizarre effects are attributed to movement of the electrode by the heart.

5. The lower end of the esophagus, as judged from a series of controls, is an unfavorable position for the application of the exploring electrode in clinical electrocardiography because of the diversity of patterns found in normals and the apparently hopeless task of standardization of curves for that area. The "endocardial pattern" of potential variation recorded at the auricular level of the esophagus deserves further investigation.

6. We have found no position, or combination of positions, for the application of an exploring electrode below the diaphragm, either on the body surface or within the lumen of the digestive tract, which is superior to the left leg for the study of ventricular electrical activity, although any position below the level of the umbilicus can be used to demonstrate the same pattern.

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A STUDY OF METHODS OF MAKING SO-CALLED UNIPOLAR ELECTROCARDIOGRAMS

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THE almost simultaneous demonstration that chest leads are capable of reflecting the presence of injury in certain parts of the heart when limb leads fail to do so,[1] and that the order of excitation of the human ventricles in bundle branch block can be ascertained by chest leads far better than by limb leads[2] raised new problems in electrocardiography which have not as yet been completely solved. The obvious deficiencies of limb leads and the equally obvious necessity for the use of chest leads, at least as a supplement to limb leads, made it seem desirable to try to learn more about the distribution of potential of cardiac origin on the body surface. Such information is essential if electrocardiographic procedures are to rest upon a scientific basis instead of continuing to rest upon empiricism or unverified assumptions.

In order to study such problems it is first of all necessary to have a method, or methods, by which the potential transmitted to an exploring electrode as a result of cardiac action currents is not materially distorted in electrocardiograms by the potential transmitted to the electrode or system of electrodes with which the exploring electrode is paired. At least three attempts have been made to develop "unipolar" leads in man. The methods used have had to rest upon assumptions, the validity of which remains open to question.

Wilson,[3] in his central terminal method (which, for brevity, we shall refer to as the CT method), subtracts in effect the mean potential of the right arm, left arm, and left leg from that of the exploring electrode. In order to conclude that by such a procedure he records the potential of the exploring electrode, he must assume, as he has pointed out, the validity of the Einthoven equilateral triangle hypothesis.

Molz[4] immersed all of the body except the head in a conducting fluid bath (Leitungswasser) lined by a copper network, and assumed, as the result of experiments with a model, which are not pertinent to the problem, that the potential of the network remained constant.

Eckey and Fröhlich[5] modified Molz' procedure in a variety of ways. The body was completely immersed in distilled water (so that presumably all of the electrolyte in the water was that derived from the body surface) and completely surrounded by a copper network within

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Received for publication March 23, 1944.

the fluid bath. The proof offered by these workers that the potential of their network remained constant (so that a unipolar lead could be obtained by pairing the network and some body area) was that a difference in potential of cardiac origin could be demonstrated between the copper network and the water inside (which surrounded the body), whereas no difference in potential could be demonstrated between the copper network and the water outside the network. They state that the results obtained by their procedure differed materially from those of Molz, but were in good agreement with those of Wilson's CT method. This latter observation was confirmed by Burger.[6] In a recent paper, Wilson[7] has stated in effect that such studies "demonstrated" that the largest potential variation of the central terminal does not ordinarily exceed 0.3 millivolt. It therefore becomes a matter of some importance to inquire into the validity of Eckey and Fröhlich's procedure in an effort to ascertain whether Wilson's method, which at least has the advantage of being practical for clinical electrocardiography, may be accepted as valid, or whether both procedures are still to be regarded as open to question.

EXPERIMENTS ON ECKEY AND FRÖHLICH'S IMMERSION PROCEDURE FOR OBTAINING "UNIPOLAR" LEADS

An enameled pan approximately 20 inches long, 8 inches wide, and 6 inches deep was filled nearly to the top with distilled water. A sheet of bronze fly-screening was molded into the form of a bowl with a diameter at the top of approximately 6 inches. It was placed in the distilled water bath, the sides of the screen being high enough so that the water inside was completely screened from the water outside. The screen was insulated from the pan by rubber sheeting. The right arm lead wire of the electrocardiograph was attached to the screen. The forefingers of both the right and left hands were placed in the bath inside the screen about 5 inches apart, near opposite sides of the screen, and an electrode attached to the left arm lead wire was placed in the bath inside the screen about ¼ inch from the forefinger of the right hand. The sensitivity of the apparatus was adjusted so that 1 mv. = 3 cm. The tracing obtained is shown in Fig. 1, *A-1*. The left arm electrode was then removed to the bath outside the screen, under which circumstances no difference of potential developed (Fig. 1, *A-2*).

The above results are identical in principle with those obtained by Eckey and Fröhlich[5] with respect to the potential of the network and the water inside and outside the network, and constitute all of the evidence adduced by these authors to demonstrate that the potential of the network remains constant. If such evidence proves that the potential of the network in Eckey and Fröhlich's procedure remains constant despite the fact that a human body was inside their network, it would also prove that the potential of our screen remains constant when

a part or parts of the body are in contact with the water inside the screen. As a matter of fact, the evidence cited above does not prove that the potential of Eckey and Fröhlich's network or of our screen remains constant, but is irrelevant to that problem. There is reason to predict that, in the Eckey and Fröhlich procedure, the relative nearness of a part of the body to the screen will influence the differences of potential of cardiac origin which develop between the surface of such a part and the screen. If this is the case, the procedure is obviously useless as a method for making unipolar electrocardiograms. The probability of occurrence of this phenomenon can be tested by a simple experiment, using the model we have described above.

A long needle electrode, insulated except at the tip and connected with the right arm lead wire, was strapped to the right forefinger in such a way that, when the finger was placed in the water bath, the electrode was completely insulated from the bath. Thus, the finger constituted the sole source of potential variation of cardiac origin transmitted to this electrode. An electrode attached to the screen was connected with the left arm lead wire. Both the right and left forefingers were placed near the middle of the water bath inside the screen, each to a depth of approximately 1 cm., and approximately 1 cm. from each other, and an electrocardiogram was made (Fig. 1, *B-1*). The right forefinger, inserted to approximately the same depth as before, was then moved to within 1 cm. of the edge of the screen, and the electrocardiogram was repeated (Fig. 1, *B-2*).

The above experiment demonstrates that, despite the fact that no differences of potential developed between the screen and the part of the water bath outside the screen (tested in each instance as in Fig. 1, *B-3*), moving the right forefinger from a position near the middle of the part of the bath inside the screen to a position much nearer a part of the screen, while the left forefinger remained in a relatively constant position, caused definite changes in the differences of potential between the right forefinger and the screen. Whether these changes are due to changes in the potential variations of the electrode attached to the screen, or the electrode attached to the finger, or both, is of no great importance in so far as the validity of the method is concerned. The fact that the electrode on the finger was insulated from the water suggested that the change in potential variations was in the electrode attached to the screen. This view is supported by various other experiments, of which one is described herewith.

If an electrode attached to the left leg is connected with the left leg lead wire, and an electrode attached to the screen is connected with the right arm lead wire, and the right forefinger is placed in the part of the water bath inside the screen, an electrocardiogram made under such conditions resembles Lead II (Fig. 1, *A-3* and *A-4*). If, however, the

right forefinger is replaced by the left forefinger, the electrocardiogram resembles Lead III (Fig. 1, *A-5* and *A-6*). These results are what one would expect if the potential variations of the finger in the bath were transmitted to the screen. They would be difficult to explain in any other way.

From the observations in the various experiments described above, it seems to us proper to conclude that the reason advanced by Eckey and Fröhlich to support the claim that their *immersion procedure* can be used to obtain unipolar leads has no merit. We are therefore not greatly moved in favor of the CT procedure by Wilson's assertion that studies made by Eckey and Fröhlich's procedure "demonstrated" that the potential variations of the central terminal do not usually exceed 0.3 millivolt. The current flow in water with a low electrolyte content and in a network seems to be about what would have been anticipated from established laws of physics.

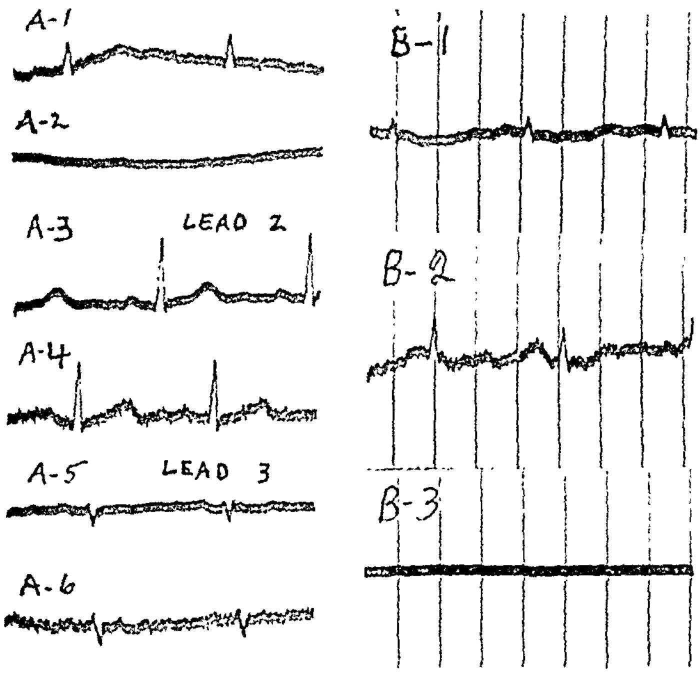

Fig. 1.—See text for explanation of illustrations.

The dubious status of Eckey and Fröhlich's procedure emphasizes the importance of attempting to obtain at least some evidence bearing on the accuracy of Wilson's CT method before accepting it. It occurred to us that there might be some value in comparing certain results obtained by CT "unipolar" leads with those obtained by pairing the exploring electrode with one placed over the spine of the right scapula (which, for brevity, we shall call the RS method). This latter procedure, as we have demonstrated by comparison with the method of balanced potentials,[8, 9] produces less subtraction or interference effects on the potential variations of the exploring electrode than is produced by pairing it with either the right or left arm.

COMPARISON OF THE CENTRAL TERMINAL METHOD FOR RECORDING THE POTENTIAL VARIATIONS OF AN EXPLORING ELECTRODE WITH THE METHOD OF PAIRING THE EXPLORING ELECTRODE WITH ONE PLACED OVER THE SPINE OF THE RIGHT SCAPULA

In 1934, when Wilson and his associates[10] reported studies of bundle branch block in which the CT method was used, the following statements appeared: "A second peculiarity of the precordial curves in right branch block is the prominent upstroke at the beginning of QRS in the leads taken furthest to the right. This deflection occurs in canine as well as in human curves. No similar deflection is present in direct curves from the right ventricle of dogs with right branch block. For the time being the origin of this summit remains obscure." The upstroke referred to in the above quotation, because of the polarity used at that time, represents relative negativity of the exploring electrode, and would be a downstroke with the polarity used at present. In a recent paper by Wilson and his associates,[7] in which the electrocardiographic abnormalities in right bundle branch block are described, we were unable to discover any reference to the unexplained deflection in leads made over the right side of the precordium by the CT method. It is nevertheless well illustrated in Figs. 11, 12, 14, and 15 of that paper. We shall attempt to show in a part of the evidence to be presented that this deflection has a significant bearing on the validity of Wilson's "unipolar" leads.

It is generally assumed that the potential variations of an epicardial area are so much greater than those of other parts of the body away from the heart that leads made with one electrode on the epicardium and the other on some area away from the heart are in effect unipolar leads.[7] This view is supported by the fact that the position of the distal electrode has little influence on the form of such an electrocardiogram. On the other hand, a change in the position of the distal electrode is capable of modifying the form of the *precordial* electrocardiogram, although in general these curves are determined mainly by the position of the exploring electrode. It is also assumed by many workers, both from theoretical considerations and from the results of experimental observations, which need not be reviewed here, that the potential of a precordial area is dominated by the action currents flowing in the part of external cardiac surface nearest to it. We know of no evidence not in accord with this assumption. Obviously, however, one would expect decrement in the magnitude of potential variations as the distance from the heart increases (which seems to have been clearly confirmed by experiment), and, equally obviously, the ratios of distance between the electrode and various parts of the heart are altered as the electrode is moved from contact with the heart to some point farther away. Thus, while there may be a resemblance between an epicardial lead and one

from the overlying precordium, they may have important differences qualitatively as well as quantitatively. It follows, therefore, that a material difference in form between an epicardial and overlying precordial lead may result from (1) a difference in the potential variations transmitted to the exploring electrode because of the fact that, when electrodes of the same size are used, the precordial electrode is materially influenced by a relatively larger area of the epicardial surface, or (2) in precordial leads, the distal electrode or set of electrodes may no longer be relatively indifferent, so that the precordial lead is, to a certain extent, a subtraction or interference curve.

The second of the above-mentioned possibilities, namely, that Wilson's "unexplained deflection"[10] is derived from the central terminal, does not seem to have been tested. If evidence could be obtained that the potential of the central terminal does not remain constant during the heartbeat, it would open to question the value of Wilson's method for recording the potential variations of single areas, and particularly of positions so far from the heart as the extremities. Thus, Wilson's conclusion that the potential of the right arm is conspicuously negative throughout the greater part of the QRS interval might be one of a series of incorrect statements. This is due to the fact that, when the exploring electrode is placed at a distance from the heart, the form of the electrocardiogram might not only be influenced by the potential variation of the central terminal, but might actually be dominated by it, if the potential variation transmitted to the exploring electrode happened to be of relatively small magnitude. It is of vital importance to electrocardiography that, if error in matters of this nature exists, such error be recognized. If, on the other hand, there is no important source of error in Wilson's "unipolar" leads, they should be used for practically all electrocardiographic work. We shall therefore inquire into the credibility of assumptions which must underlie "unipolar" leads and also those which must underlie our RS method. We shall then present the results of certain tests of the ability of these methods to demonstrate distribution of potential variation in accord with the underlying assumptions.

The Assumptions Underlying the RS and CT Methods.—We have emphasized in previous publications[8, 9] that two assumptions have to be made to establish our balanced potentials procedure and its simpler substitute of pairing the exploring electrode with one placed over the spine of the right scapula (RS method) as methods of recording the potential variations of an exploring electrode. The first is that an approximate balance of potentials among the positions on which electrodes are placed, with their varying patterns of potential variation, cannot occur consistently by chance throughout the entire ventricular complex, although it might readily occur by chance at a single instant. It has seemed to us to be safe to make this assumption. The second assumption is that, along surface lines extending from the right and left

borders of the heart to the corresponding shoulder, there is no part of the potential variation that is not subject to decrement as distance from the heart increases. It is recognized that the validity of this second assumption does not have to be conceded. The magnitude of the error involved in this assumption measures the error of the method of balanced potentials as a unipolar procedure (plus a slight additional error, usually not exceeding 1 mm. for any part of the ventricular complex, because of the combination of technical fault and discrepancy between the prediction of accurate preservation of pattern and experimental observations).

It is essential to the Einthoven equilateral triangle hypothesis that the trunk function as a homogeneous fluid volume conductor, and it is therefore inevitable, if that hypothesis be valid, that all potential variations be subject to decrement as distance from the heart increases.[11] Consequently, our second assumption is a necessary part, but by no means the whole, of only one of the assumptions which underlie the CT method. If our assumption, which, however, does not require that the body function as a homogeneous fluid volume conductor, is not valid, neither procedure requires further consideration. If, on the other hand, the second assumption we have made is valid and the results obtained by this method and Wilson's CT method differ materially—which they do in most cases*—there seems to be no possibility that the assumptions which underlie the Einthoven hypothesis are all valid, or that the CT method is justified.

Among the various reasons for suspecting that the Einthoven hypothesis is subject to enormous error are the easily demonstrable differences in decrement of potential variation above and below the diaphragm as distance from the heart increases. We have already published studies which illustrate this fact in man, and have shown in experimental animals that there is comparatively little decrement between positions so near the heart as just below the diaphragm, and the left leg,[9] although, in man, there may be appreciable decrement on the surface of the back.[12] Against this may be contrasted the very rapid decrement found on the front of the chest[4, 9] or in the esophagus above the level of the heart. The distribution of potential on the upper part of the human abdomen seems to be complex, but there is definite evidence to indicate that in this area there is rapid decrement of the precordial patterns as distance from the heart increases. In the same area there is probably fairly uniform distribution of the diaphragmatic pattern, similar to the distribution of this pattern to other positions below the diaphragm in man and to the entire body surface below the diaphragm in dogs.[9] If this be the case, we have one pattern of potential fairly uniformly distributed on the upper part of the abdomen, and another subject to rapid decrement. This behavior raises a question as to the

*The potential of Wilson's central terminal and that of an electrode over the spine of the right scapula are occasionally nearly the same throughout either the QRS complex or the T wave, but rarely throughout both.

justification of an assumption that there is no uniform distribution of a potential pattern to all regions above the diaphragm. Such an assumption, if valid, would mean, as stated above, that approximately unipolar leads could be recorded by the method of balanced potentials. If it is not valid, the method of balanced potentials merely reduces interference with the potential variations of the exploring electrode by eliminating the potential variations concerned in the formation of Lead I, irrespective of whether the electrodes by which the balance is achieved are on the right or the left side.

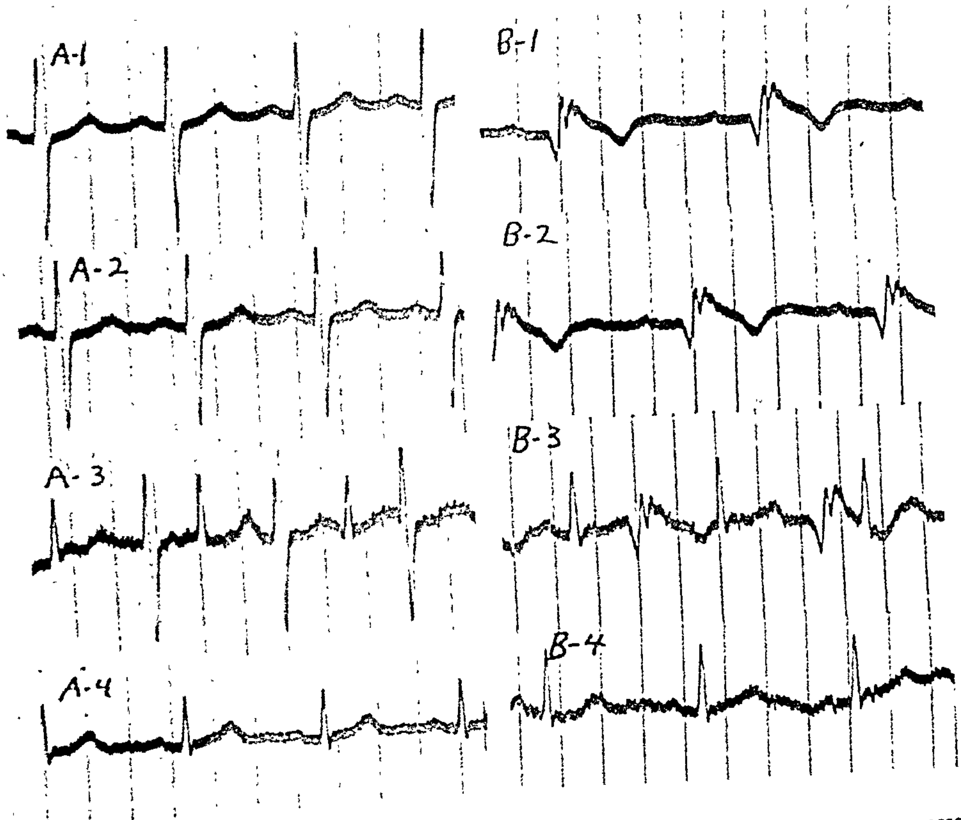

Fig. 2.—*A-1* is the CR_4 lead of Subject 1. In *A-2*, the electrode was removed from the precordium of Subject 1 and was placed on the right arm of Subject 2; contact between the two subjects was maintained by placing the right forefinger of Subject 2 on the C_4 chest position of Subject 1. In *A-3*, the contact between the two subjects was maintained, but the electrode was moved from the right arm to the left leg of Subject 2. In *A-4*, the electrode which, in the preceding experiments had been on the right arm of Subject 1, was removed to the right arm of Subject 2, thus recording Lead II of that subject.

In the *B* series the same set of experiments was performed except that the C_2 chest position was used for the point of contact between the two subjects. Subject 1 of these experiments had a typical right bundle branch block. These observations show that the potential variations of the point of contact of each subject with the other are uniformly distributed throughout the body surface of the other subject. Apparently each body functions as a nonpolarizable electrode for its area of contact with the other subjects.

If it be assumed that there is uniform distribution of a potential pattern to all positions above the diaphragm, this pattern is not eliminated by the method of balanced potentials, and is therefore also present but not recognized over the spine of the right scapula. Such a pattern will be subtracted quantitatively from the potential variations of an exploring electrode in electrocardiograms made when the latter is placed below the diaphragm. Unless the pattern uniformly distributed above the diaphragm is qualitatively the same as that below the diaphragm, however, the configuration of the electrocardiogram must necessarily

change as the amplitude of recorded deflections increases or decreases. Studies of the intricate patterns of bundle branch block made in our laboratory by the RS method, which tend to exhibit relatively smaller deflections in the right flank and back and slightly larger deflections in the left flank than in the left leg, show excellent preservation of pattern in all these positions. In the recent study referred to above,[12] it has been demonstrated by the RS method that the pattern recorded from the left leg and from positions so near the heart as the fundus of the stomach or the lower end of the esophagus may be practically identical, except for a marked increase in the size of deflections at positions near the heart. These observations would seem to rule out the likelihood, although not the possibility, that any pattern other than the one recorded is concerned.*

One of the assumptions required by the Einthoven hypothesis is that the attachments of the extremities are far enough away from the heart that electrical activity in one part of that organ possesses no advantage, by virtue of its relative distance, over electrical activity of any other part in exerting an influence on the potential variations of an extremity. We have shown by the method of balanced potentials, by the RS method, and by pairing the electrodes about the attachments of the arms† that the pattern of potential variations of the right arm is usually similar to that of the right side of the precordium, except that the deflections are very small.[8, 9] It was shown by the same methods that the pattern of potential variation of the left arm is similar to that obtained from a position just outside the left border of the heart. Moreover, as was stated above, it has been shown by the RS method that the pattern of potential variations of the left leg is similar in the great majority of cases to the pattern recorded from the duodenum or from parts of the stomach, and not infrequently to patterns recorded from the lower end of the esophagus.[12] Furthermore, cardiac injury leading to the development of abnormality in one of these patterns does not necessarily cause abnormality in the other patterns (unpublished observations). Such relations we regard as one of the many observations which are incompatible with the Einthoven hypothesis.

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*Potential variations uniformly distributed throughout areas to which electrodes are applied obviously cannot be detected, for we measure only difference of potential. This fact exposes to error any so-called unipolar lead made under conditions where such a possibility exists. This can be demonstrated by the following simple observation. If contact is made between two subjects with skin resistance low enough for currents to flow freely, the mean potential of that part of one subject in contact is uniformly distributed throughout the other subject. This phenomenon is not detected by any method of pairing electrodes on one subject alone. It is necessary to place the exploring electrode at the point of contact, and after contact has been made, at various positions on the body of the second subject, observing the similarity of patterns recorded (with such connections on the two bodies, an electrocardiogram of the second subject will also be recorded). These phenomena are illustrated in Fig. 2.

†This procedure corresponds in principle to Groedel's partial electrocardiograms,[15] which led him to conclude that the potential of the right arm is derived from the right ventricle, and that of the left arm from the left ventricle. In reality, the potential variations of the right arm are dominated by the action currents occurring at the anterior surface of the right ventricle (which in turn are derived in part, at least, from electrical activity in the left ventricle), and the potential variations of the left arm are dominated by the action currents at the anterolateral wall of the left ventricle (which likewise are derived in part from activity in the right ventricle).

Studies on the electrical characteristics of tissues[13-15] in attempts to obtain evidence whether they behave in a manner consistent with the assumption that the body functions as a homogeneous fluid volume conductor have led to conclusions which are not in full agreement. In fact, only one of these studies[15] seems to offer any support to the assumption, but since no attention is paid to the relationships of tissues to each other as they occur in the human body, the possible significance of that study from our present viewpoint remains to be decided.

From the foregoing discussion, we conclude that such tests as have been made of the assumptions required to support the prediction that the mean potential of the right arm, left arm, and left leg will remain approximately equal to zero throughout the cardiac cycle,* instead of confirming the validity of that prediction, tend to increase the doubt concerning it. It is therefore necessary to obtain further evidence, which can be done by direct comparison of some of the data obtained by the CT and RS methods in a study of the distribution of potential of cardiac origin.

Comparison of Results Obtained by RS and CT Methods.—In the observations to be reported below, in which certain results of the two methods are to be compared, both the central terminal and an electrode on the spine of the right scapula were paired with the same exploring electrode so that there could be no question as to the sources of differences in the tracings or the time incidence of deflections. A resistance of 50,000 ohms was interposed between each of the electrodes connected with the central terminal and the terminal itself. Three types of observations were made in this study.

Observation 1.—If the unexplained upward (downward, according to the polarity used at present) deflection recorded from the right side of the precordium in right bundle branch block results from potential variations of the central terminal, the following may be expected to be true:

a. The unexplained deflection will not be subject to decrement as the exploring electrode is moved toward the right shoulder, although the potential transmitted to the exploring electrode may be subject to decrement.

b. The differences in potential between the central terminal and a relatively more constant potential will include part or all of the unexplained deflection.

c. The potential variations of the right side of the precordium recorded by a more accurate method should resemble those found over the epicardium of the right ventricle of the dog more closely than those of the CT method, in that the unexplained deflection will be either absent or smaller.

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*The sum of the differences of potential between the central terminal and electrodes on each of the three extremities obviously must equal zero. Failure to take into account this simple mathematical relationship might lead one to think that he had experimental confirmation of the validity of the CT method.

In Fig. 3 the following points, representative of results in six cases, are illustrated:

1. The "unexplained deflection" is present in a case of right bundle branch block, just as Wilson[10] found it when the right side of the precordium is paired with the central terminal (*A-1*). It does not decrease in size as the exploring electrode is moved to successive positions farther from the heart in the direction of the right shoulder,* although the other parts of the QRS complex are subject to decrement (*A-2* and *A-3*). On the right arm this unexplained deflection is greater in amplitude than any other deflection of the QRS complex, and actually dominates the pattern (*A-4*).

2. The unexplained deflection is present in a lead made by the CT method with the exploring electrode placed over the spine of the right scapula (*B* series).

3. Leads made by the RS method with the exploring electrode on the C_1 position, the right arm, and intermediate positions fail to show the unexplained deflection, and, to this extent, resemble the tracings which Wilson obtained from the right side of the heart in canine bundle branch block (*A* series).

Observation 2.—Decrement as an exploring electrode is moved from the right side of the precordium in the direction of the right shoulder can be demonstrated by any method of pairing electrodes, provided the distal electrode or set of electrodes is placed at a distance from the heart. If the distal electrode makes a contribution to the electrocardiogram, this contribution will be relatively greater as distance of the exploring electrode from the precordium increases and interference with the pattern of the exploring electrode correspondingly increases. Consequently, the method by which integrity of patterns is best maintained probably records tracings with the least interference from the distal electrode or central terminal. Figs. 3 and 4 illustrate the superiority of the RS method over the CT method in reflecting the integrity of pattern as the distance of the exploring electrode from the heart increases (Figs. 3, *A*, *C*, and *D* series. Fig. 4, *A*, *C*, and *D* series).

Observation 3.—If electrodes are paired by placing the distal electrode on the tip of the right acromial process and the exploring electrode on the right anterior axillary fold, the resulting electrocardiogram resembles the pattern of potential variations of the right arm as obtained by the RS method, and usually does not resemble the pattern obtained by the CT method (Figs. 3, *A-4* and *A-5*, *D-4* and *D-5*; Fig. 4, *A-3* and *A-4*, *C-4* and *C-5*). Similar relationships are found when electrodes are paired in the same way about the attachments of the left arm. The agreement between RS and CT methods is better for the left arm than the right because the potential variations of the left arm are usually greater, and the potential variations of the "indifferent electrode" are

*It actually seems to increase in size because of lessening of the neutralizing effect of positive potential variation derived from the exploring electrode.

relatively less able to distort the pattern of the exploring electrode (Fig. 3, *C* series).

DISCUSSION

In the past there has been no means by which the probable validity of the CT method of making unipolar leads could be tested, although attempts have been made to use the immersion procedures for that purpose. There is no completely satisfactory method now, and perhaps because of the impossibility of being certain that one is recording the potential variations of a single electrode, none can be devised with apparatus now available. Nevertheless, as we have tried to show, it is possible, by comparing certain differences in results obtained by the CT and RS methods, to secure data which have a definite bearing on the validity of the two procedures. In this study we have concentrated our attention, as discussed in detail below, on (1) the comparative ability of the two methods to demonstrate preservation of certain patterns of potential variation as recorded from positions near the heart and from other positions much farther from the heart, (2) a comparison of the results obtained in recording the potential variations of the upper extremities by these methods and by pairing electrodes across the attachments of the arms, and (3) the behavior of Wilson's "unexplained deflection" in right bundle branch block,[10] as illustrated by the CT and RS methods.

1. Both methods can be used to demonstrate that, along a line from the right side of the precordium to the right shoulder and a similar line from just outside the left border of the heart to the left shoulder, decrement in potential variations occurs as distance from the heart increases, and that there is a tendency toward preservation of a pattern recorded near the heart. The superiority of the RS method over the CT method in preserving the pattern at positions along both lines is illustrated in Figs. 3 and 4. If one is to assume that the CT method is the more accurate of the two, one must also assume that the better preservation of the pattern by the RS method is a remarkable coincidence resulting from the interference of potential variations derived from the electrode placed over the spine of the right scapula. It would probably be conceded that no great error is involved in regarding the pattern of potential variations transmitted to the latter electrode as similar for each heart beat. If so, we believe there would be considerable difficulty from the mathematical viewpoint in defending the assumption that the preservation of the pattern with decrement results from interference arising from the electrode placed over the spine of the right scapula. Thus, it seems safe to conclude that decrement with preservation of pattern must reflect potential variation of the exploring electrode. On the other hand, there are no difficulties encountered in the assumption that the inferiority of the CT method for the demonstration of preservation of patterns with decrement results from a

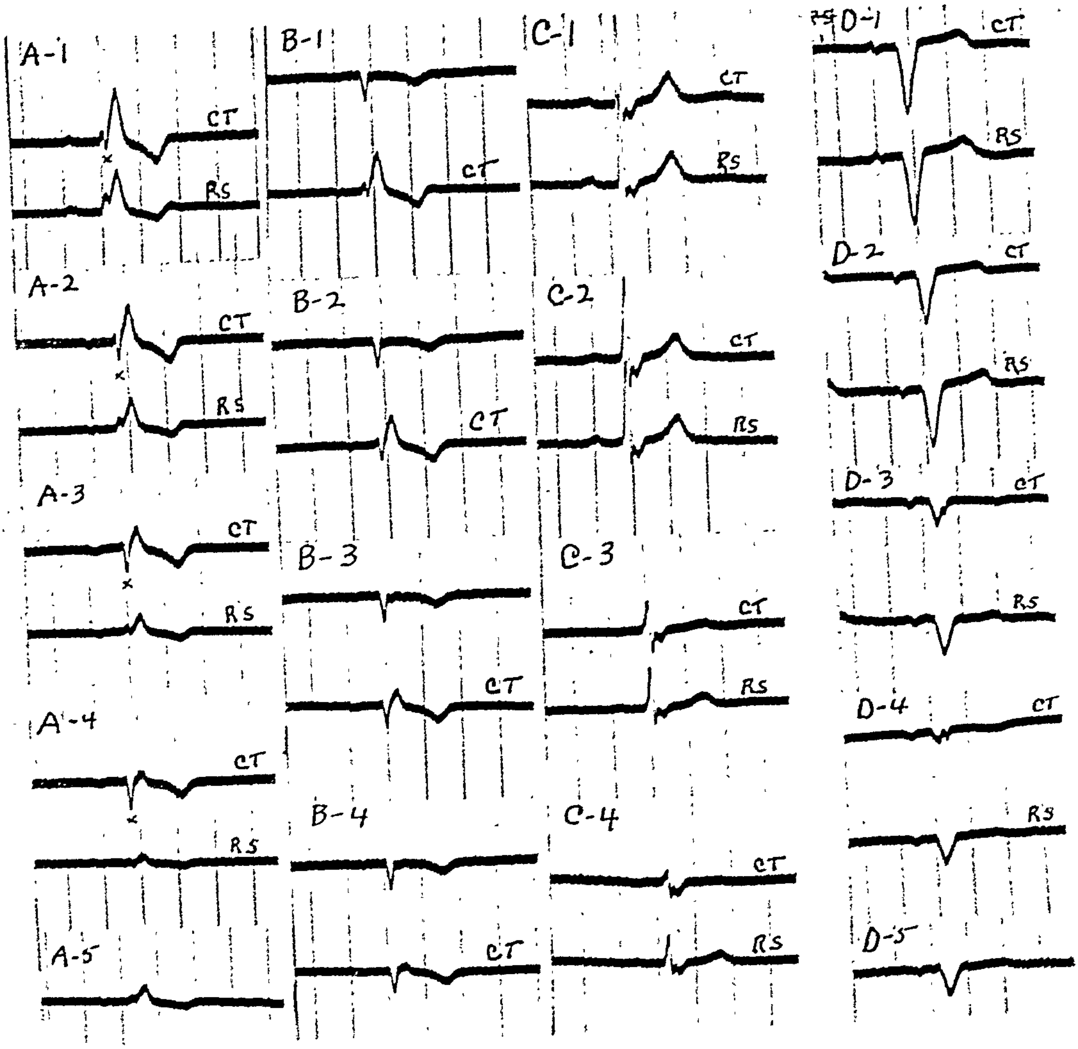

Fig. 3.—All of the tracings in series *A*, *B*, and *C*, were made from a patient with right bundle branch block. In *A-1*, the exploring electrode was placed on the C_1 chest position and paired both with the central terminal CT (50,000 ohms resistance being interposed between each electrode on a limb and the central terminal in all experiments) and with an electrode on the spine of the right scapula, RS. Note the "unexplained" early deflection, marked "*x*" in the CT lead. In *A-2*, the exploring electrode was moved 1½ inches in the direction of the right shoulder, in *A-3* an additional 1½ inches, and, in *A-4*, it was placed on the right arm. In *A-5*, the exploring electrode was placed on the right anterior axillary fold and paired with an electrode over the tip of the right acromial process.

In the *B* series, the central terminal leads, CT, were made like those of the *A* series, and each was recorded simultaneously with a CT lead made with an exploring electrode on the spine of the right scapula. The "unexplained" deflection constitutes the only major difference of potential, during the QRS complex, between the central terminal and the spine of the right scapula.

In *C-1*, the exploring electrode was placed slightly above and to the left of the C_2 chest position, and paired with the central terminal, CT, and the spine of the right scapula, RS. In *C-2*, the exploring electrode was moved 1½ inches in the direction of the attachment of the left arm, in *C-3*, 1½ inches further in the same direction, and, in *C-4*, on the left arm.

The tracings in the *D* series were obtained from a patient with left bundle branch block. In *D-1*, the exploring electrode was placed on the C_1 chest position, and paired with the central terminal, CT, and the spine of the right scapula, RS. In *D-2* and *D-3*, the exploring electrode was moved to successive positions 1½ inches nearer the attachment of the right arm, and, in *D-4*, it was placed on the right arm. In *D-5*, the exploring electrode was placed on the right anterior axillary fold and paired with an electrode over the tip of the right acromial process.

constant error caused by the recurrence of potential variations in the central terminal. On the basis of this assumption, the smaller the potential variations of the exploring electrode become, the greater the distortion of the pattern, which is in agreement with the experimental data.

2. In Figs. 3 and 4 the comparison between the patterns of differences of potential recorded by pairing electrodes across the attachments of

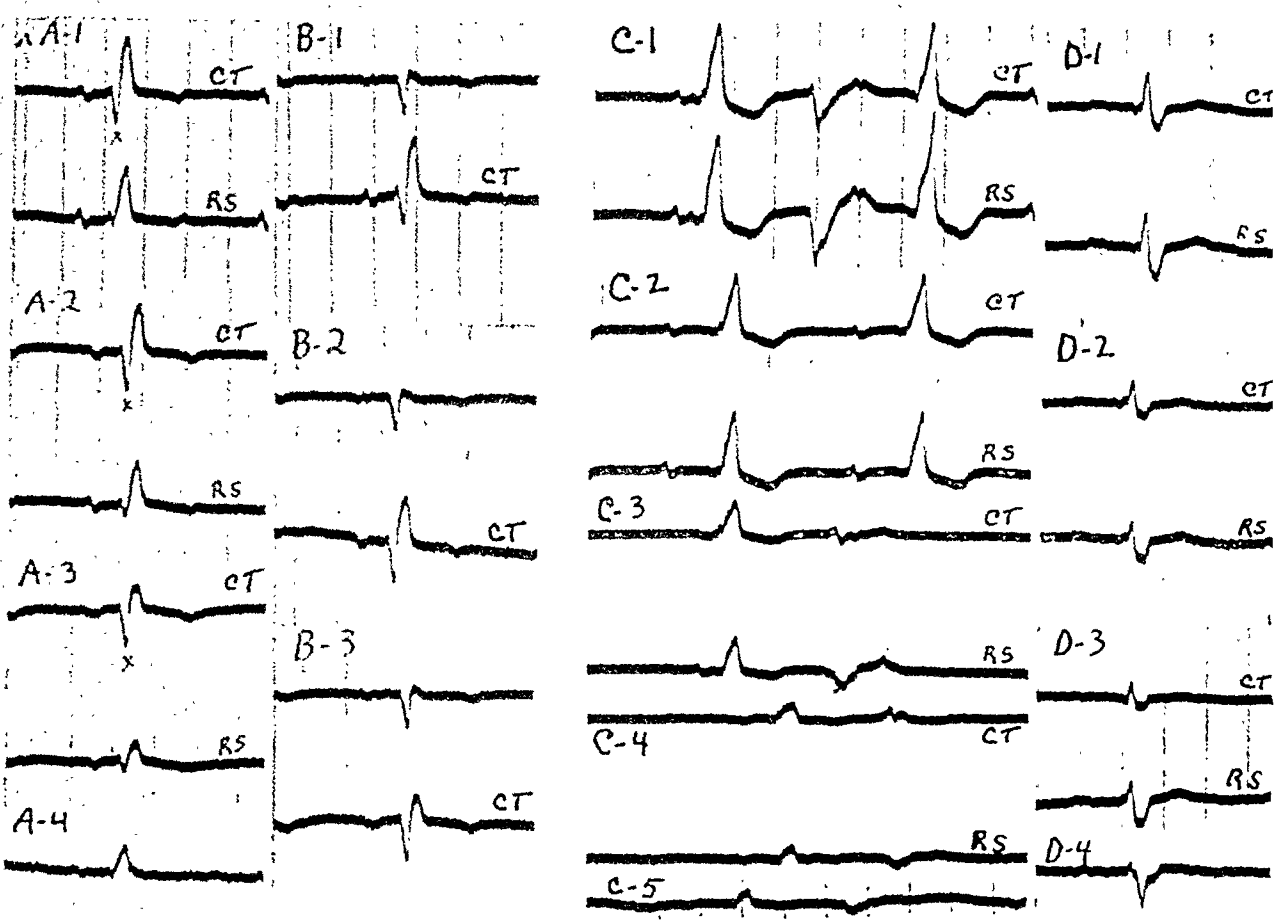

Fig. 4.—The tracings in the *A* and *B* series were obtained from a patient with right bundle branch block. In *A-1*, the exploring electrode was placed on the C_1 chest position and paired with the central terminal, CT, and with an electrode on the spine of the right scapule, RS. In *A-2*, the exploring electrode was moved to a position approximately midway between the C_1 chest position and the attachment of the right arm, and, in *A-3*, it was placed on the right arm. In *A-4*, the exploring electrode was placed on the right anterior axillary fold and paired with an electrode on the tip of the right acromial process. Note that there is a large "unexplained" deflection "*x*" early in the QRS complex of the CT leads and a small "unexplained" deflection in RS leads, neither of which is subject to decrement as the exploring electrode is moved farther from the heart, and that this deflection is insignificant in the lead made by pairing electrodes across the attachments of the right arm.

In the *B* series, the CT leads were made as in the *A* series. The upper lead of each group was obtained by pairing an exploring electrode on the spine of the right scapula with the central terminal. The "unexplained" deflection represents the chief difference of potential between the central terminal and the spine of the right scapula, although the T-wave potential of the latter position is relatively slightly negative to that of the central terminal. The tracings in the *C* and *D* series were obtained from a patient with right bundle branch block and ventricular extrasystoles. In *C-1*, the exploring electrode was placed on the C_1 chest position, and paired with the central terminal, CT, and with an electrode over the spine of the right scapula, RS. In *C-2*, the exploring electrode was moved 1½ inches in the direction of the attachment of the right arm, in *C-3*, 1½ inches further in the same direction, and, in *C-4*, to the right arm. In *C-5*, the exploring electrode was placed on the right anterior axillary fold and paired with an electrode placed over the tip of the right acromial process.

In *D-1*, the exploring electrode was placed on the C_5 chest position, and paired with the central terminal, CT, and with an electrode over the spine of the right scapula, RS. In *D-2*, the exploring electrode was placed midway between the C_5 chest position and the attachment of the left arm, and, in *D-3*, on the left arm. In *D-4*, the exploring electrode was placed on the left leg and paired with an electrode placed over the spine of the right scapula. In this case, the potential variations of the right arm, left arm, and left leg, as recorded by the RS method, are such that the mean potential variation of the three would be small. This probably accounts for the relatively good correspondence obtained by the two methods in the case of supraventricular beats.

one of the upper extremities (anterior axillary fold and tip of acromial process) and patterns of potential variations of the corresponding area recorded by the RS and CT methods is illustrated. These are representative of results in a large series of cases (not reported here). Almost invariably there is good correspondence with the RS method for both extremities. In some cases there is fairly good correspondence with the CT method on the left side, but there is little resemblance between the two types of tracing on the right side. If it is assumed that the CT method is truly unipolar, the better correspondence between the "partial electrocardiograms" made with electrodes paired across the attachments of the arms, and the RS method for recording the potential variations of the arms must be assumed to be due to error in the method, resulting from the fact that potential variations transmitted from the spine of the scapula cause this better correspondence. Conceivably, this might apply on the right side because the difference in potential between the surfaces over the tip of the right acromion and the spine of the right scapula is slight. This explanation, however, would not apply to the better correspondence observed on the left side. A more probable explanation for these discrepancies would seem to be that the potential variations of the central terminal are greater than those of an electrode placed over the spine of the right scapula.

3. Analysis of the behavior of the "unexplained" deflection described by Wilson as being recorded over the right side of the precordium in right bundle branch block by his CT method offers, we believe, the most instructive comparison of the CT and RS methods. We have pointed out that this deflection, recorded, according to Wilson, from the right side of the precordium both in dogs and man in right bundle branch block, but not from the surface of the right ventricle in dogs, might therefore be derived from the central terminal. The fact that the unexplained deflection is either not recorded at all or is of relatively small magnitude when the potential variations of the right side of the precordium are recorded by the RS method does not tend to lessen that suspicion. The further facts that all of the deflections recorded by the RS method are subject to decrement as the electrode is moved toward the right shoulder, and that all of those recorded by the CT method except the unexplained deflection are also subject to decrement can be accounted for in only one of two ways. If the unexplained deflection is derived from the central terminal, *one would expect no* decrement as the electrode is moved farther away from the heart because the potential variations of the central terminal would not vary materially. If, on the other hand, it is transmitted by the exploring electrode and is not subject to decrement as the distance from the heart increases, it does not behave in accordance with the distribution of potential to be expected in a fluid-volume conductor. If, therefore, we accept the Einthoven equilateral triangle hypothesis, we are forced to

the contradictory conclusions that the "unexplained" deflection (1) cannot be derived from the central terminal,[8] and, (2) because of its lack of decrement at positions far from the heart, cannot be derived from the exploring electrode.[11] To avoid such an absurdity, we must discard the Einthoven hypothesis, and, with it, the sole reason for believing that the central terminal procedure ever records unipolar leads except by chance. That it actually does occasionally achieve this result with substantial accuracy in certain cases of right bundle branch block, in which the "unexplained" deflection is not recorded, we believe we have shown in Fig. 4, series *C*. Here, decrement with preservation of pattern as the distance of the exploring electrode from the heart increases is shown as well by the CT as by the RS method, in so far as beats of supraventricular origin are concerned. The CT method, however, is far inferior in demonstrating preservation of the pattern of the ventricular extrasystoles which interrupt the normal rhythm. It would appear, therefore, that the above is purely a chance result, and does not even apply to two different pathways of excitation in the same case.

If, as the evidence appears to indicate, the unexplained deflection is derived through the central terminal, the further question arises as to its source. We have made no special effort to solve this problem, but the following facts have emerged as by-products of our studies. This deflection does not appear in CR_1 leads in right bundle branch block. A somewhat similar, but small, deflection may appear in CF_1 leads, but the time relations of this deflection may be slightly different from those of the unexplained deflection. The CL_1 lead usually shows an unexplained deflection with identical time relations and with a magnitude more than twice as large as that of the central terminal lead with the exploring electrode on the same position. When extensive infarction of the left ventricle has occurred, so that the preintrinsic-intrinsic-like pair of deflections disappears from leads made with an exploring electrode placed over the left border of the precordium, the CL_1 lead may fail to show an unexplained deflection. Under these circumstances the central terminal procedure fails to record an unexplained deflection (as in Fig. 4, *C* series) or, at most, records a very tiny one. These data suggest, but do not prove, that the unexplained deflection is a left ventricular phenomenon which exerts an effect on the potential variations of the central terminal, mainly via the left arm electrode.

If we are justified in concluding that the unexplained deflection recorded over the right side of the precordium in right bundle branch block is a left ventricular phenomenon exerting its effect on leads made by the CT method via the central terminal, it would follow, because potential variations derived from the left ventricle are not usually greatly changed in right bundle branch block, that a similar error probably exists in normal cases. In our opinion, therefore, Wilson's[7] statement to the effect that the potential of the right arm is negative

throughout most of the QRS interval may be based in part on failure to take into account the possibility that a potential variation similar in magnitude to that which produces the unexplained deflection is contributed by the central terminal.

Electrocardiography has always suffered from the handicap that its results represent differences between two unknown variables. There is reason to believe that this handicap is not so serious in the case of chest leads as in the case of limb leads because of the relatively greater magnitude of potential variations at chest wall positions. Nevertheless, the possibility of error, even in chest leads, in ascribing the source of potential variation to one electrode, when, in fact, it is attributable to the other, has been demonstrated in this paper. The struggle toward the objective of an approximately accurate unipolar lead is far from over, and perhaps it has just begun. If the method of balanced potentials and its simpler, although slightly less accurate, substitute of pairing the exploring electrode with one over the spine of the right scapula, marks any progress toward that objective, it can only be so because the assumptions which underlie those procedures are valid. It is at this point that the most searching examinations of this procedure, as well as procedures that are called unipolar leads, must be made.

SUMMARY

1. The reason given by Eckey and Fröhlich for stating that unipolar electrocardiograms can be obtained by their procedure of immersing the body in distilled water and surrounding it by a copper network which is also in the water bath, with one electrode on a body area paired with an electrode attached to the network, has been subjected to experimental test. Evidence is furnished that this reason is not valid. There is, consequently, no ground for believing that unipolar electrocardiograms can be obtained by such a method.

2. The central terminal procedure of Wilson for making unipolar leads has been subjected to study.

A. The good agreement which is said to exist between Wilson's central terminal procedure and Eckey and Fröhlich's immersion procedure, a point made by Wilson in support of his method, does not demonstrate the validity of the central terminal procedure because the principle underlying the immersion procedure is unsound.

B. The various assumptions which have to be made if the central terminal procedure is to be regarded as valid as a method for making unipolar leads were compared with the assumptions which have to be made to establish the method of balanced potentials (or its simpler but slightly less accurate substitute of pairing the exploring electrode with one placed over the spine of the right scapula) as a procedure for (1) making unipolar leads, or (2) reducing interference with the potential variations of the exploring

electrode. Certain observations regarding the distribution of potential on the surface of the body cannot be accounted for on the basis of the assumptions which must underlie the central terminal procedure. No such difficulties were encountered regarding the less elaborate assumptions underlying the other procedures.

C. Certain comparisons of results obtained by the central terminal method and by pairing the exploring electrode with one placed over the spine of the right scapula have been made. (1) The latter procedure shows the phenomenon of decrement with preservation of pattern as the exploring electrode is moved away from the heart along certain lines far better than does the central terminal method; (2) the correspondence of patterns of difference of potential recorded by pairing electrodes across the attachments of the right and left arms with the patterns obtained by placing one electrode on the arm of the same side and the other on the spine of the right scapula is far closer than the "unipolar" patterns of arm potential obtained by the central terminal method, and (3) a negatively directed deflection recorded early in the QRS complex by the central terminal procedure at the C_1 position in most cases of right bundle branch block is recorded as a very small deflection, or not at all by the RS procedure. This deflection, unlike other parts of the QRS complex, is not subject to decrement as the exploring electrode is moved away from the heart. All the evidence indicates that it is derived from the central terminal. Moreover, if the assumptions which must underlie the central terminal procedure are valid, it is impossible to account for the derivation of such a deflection from either the central terminal or the exploring electrode.

3. The evidence presented indicates that, by pairing an exploring electrode with one placed over the spine of the right scapula, less interference with the potential variations of the exploring electrode occurs than in the case of methods which have been called unipolar. The bearing of this conclusion, if it be valid, on methods used in clinical electrocardiography is obvious.

We wish to thank Drs. J. H. Austin, Director of the William Pepper Clinical Laboratory, University of Pennsylvania, and L. I. Schiff, Assistant Professor of Physics, University of Pennsylvania, for valuable criticism and advice, and Dr. Franklin D. Murphy, Instructor in Medicine, for assistance in some of the experiments.

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THE EFFECTS OF ANTERIOR INFARCTION COMPLICATED BY BUNDLE BRANCH BLOCK UPON THE FORM OF THE QRS COMPLEX OF THE CANINE ELECTROCARDIOGRAM

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IN MAN the characteristic changes in the form of the ventricular complex usually produced by myocardial infarction are often greatly modified or absent when one of the two main subdivisions of the His bundle is blocked. When the conduction defect is on the left side it is rarely possible to diagnose infarction with certainty by means of either limb leads or precordial leads. Block on the right side usually prevents the occurrence of characteristic signs of anterior infarction in the standard limb leads, but not in the precordial leads. Such data as are available suggest that, as a rule, it does not seriously obscure the diganostic signs of posterior infarction, which ordinarily appear in Leads II and III.

Because the number of cases in which both bundle branch block and infarction were known to be present is relatively small, it seemed expedient to undertake an experimental study of the electrocardiographic changes produced by this combination of lesions. The methods employed in our experiments were those used in the electrocardiographic studies of infarction carried out by Wilson, Hill, and Johnston.[1]

Dogs of large or medium size were used. The heart was exposed, the right or left branch of the His bundle was cut in the usual way, and in most of the experiments the anterior descending coronary artery was ligated in its mid-portion. The chest was then carefully restored. These surgical procedures were carried out under aseptic conditions. After a period of seven to forty days, when the animal had recovered completely from the operation, the electrocardiographic observations were made. The standard limb leads and unipolar precordial leads were taken with the chest intact. Then the thorax was opened by splitting the sternum, and the anterior surface of the heart was explored by means of unipolar direct leads.

The standard limb leads of nine dogs are reproduced in Fig. 1. In the first three animals (57, 58, and 61) the right branch of the His bundle

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The observations reported in this article were made with the aid of a grant from the Horace H. Rackham School of Graduate Studies. They were summarized in a preliminary report published in the Proceedings of the Thirty-Third Annual Meeting of the American Society for Clinical Investigation, May 5, 1941 (J. Clin. Investigation 20: 460, 1941).

Received for publication May 15, 1943.

was cut, but there was no gross infarction, either because the anterior descending coronary artery was not ligated or because the attempt to occlude it was unsuccessful. The electrocardiograms of these animals are of the kind ordinarily seen in canine right branch block. Below these curves are three sets from animals (59, 62, and 66) with both right branch block and anterior infarction. It will be noted that no changes characteristic of infarction appeared in the ventricular complexes of the limb leads. In dogs with normal intraventricular conduction, infarcts similar in size and location to those induced in these experiments usually give rise to large Q deflections in Lead I.

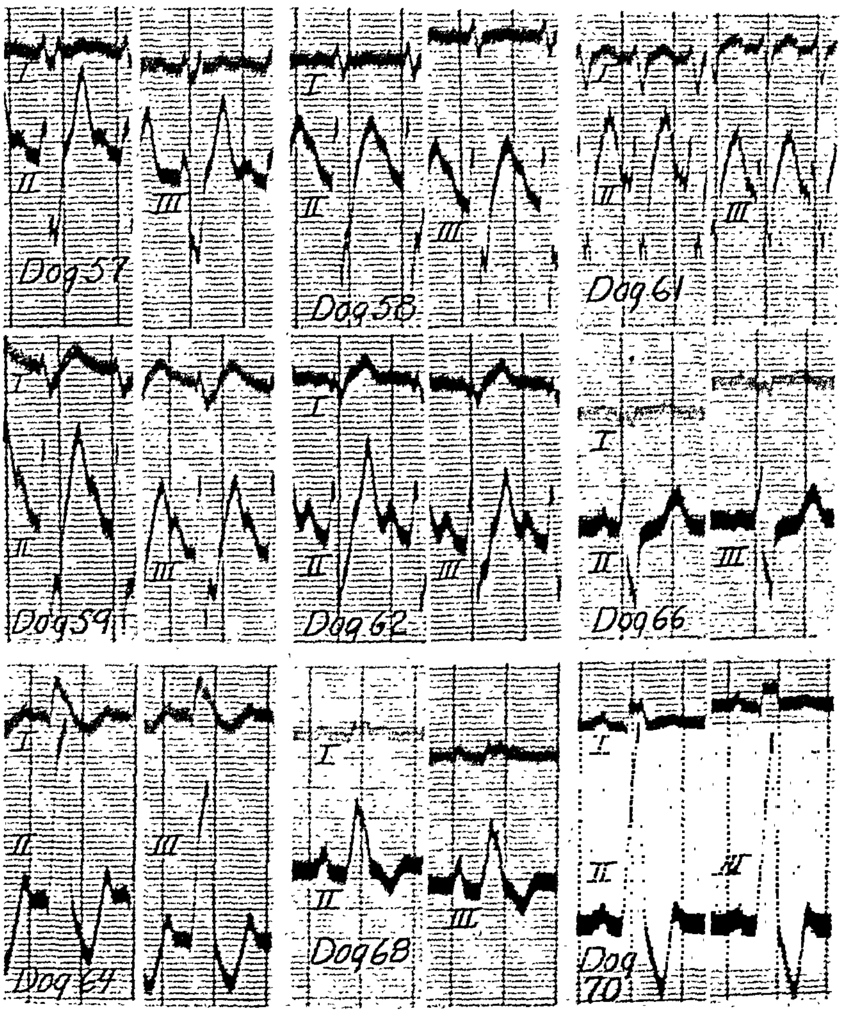

Fig. 1.—Standard limb leads with simultaneous Lead I. Upper row—three dogs with right bundle branch block. Middle row—three dogs with both right branch block and anterior infarction. Lower row—Dog 64 had left bundle branch block; Dogs 68 and 70 had left branch block and anterior infarction.

The first set of curves of the last row (Fig. 1) are from an animal (64) with left branch block only, and the second and third sets are from animals (68 and 70) with both left branch block and anterior infarction. Here also the limb leads display no changes in the ventricular complex that suggest the presence of infarcted cardiac muscle.

The precordial curves were obtained by moving the exploring electrode across the precordium in the same way as when taking comparable human curves. The exploration was begun at a point to the right of the right margin of the sternum, and was extended to a point well to the left of the apex beat. The electrode consisted of a stiff copper wire, insulated by enamel except at the ends. One end was sharpened and was brought into contact with the subcutaneous tissues by making a small slit in the skin. The enamel was removed from the opposite end for a

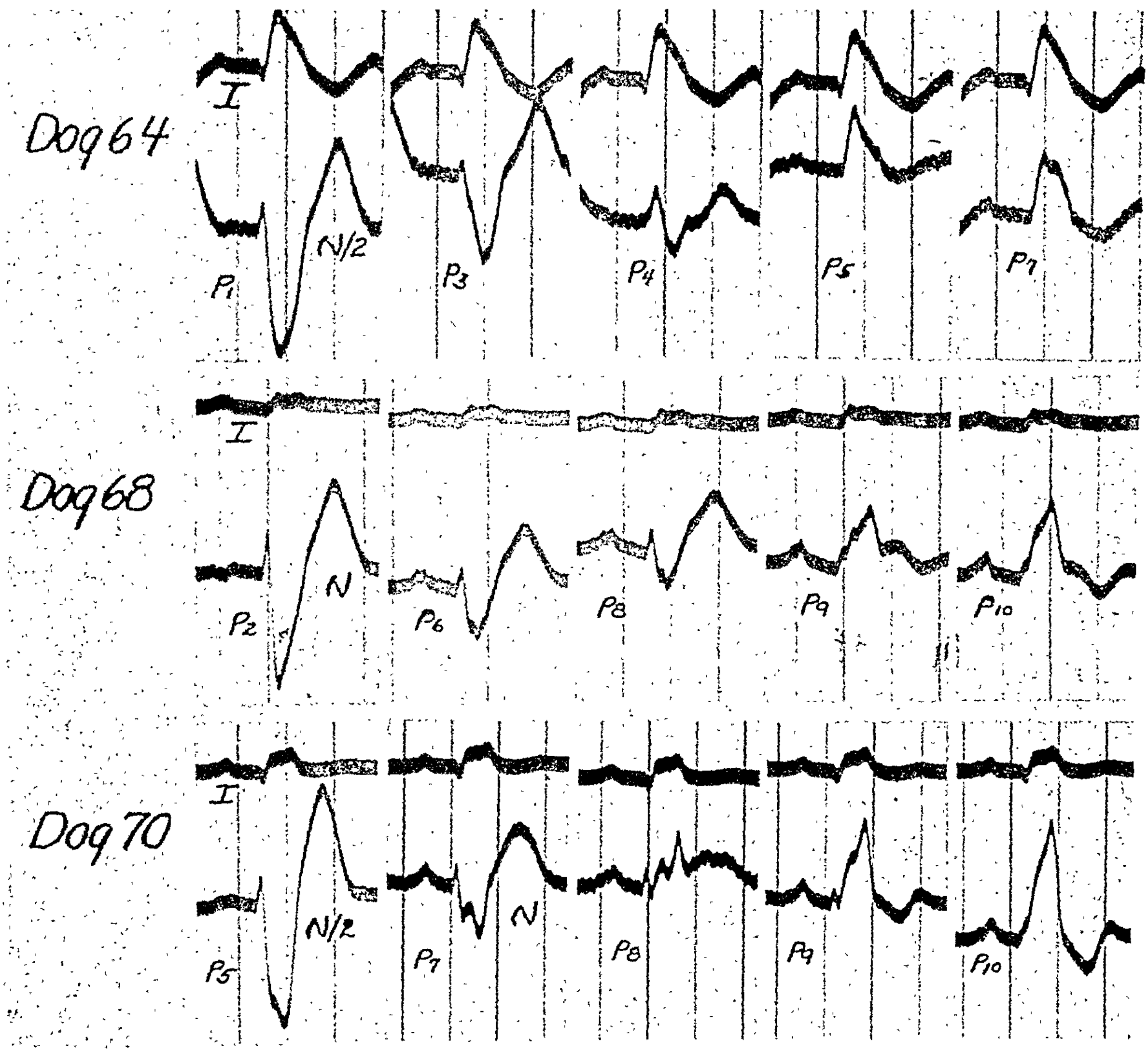

Fig. 2.—Unipolar precordial leads. Dog 64 had left bundle branch block. Dogs 68 and 70 had left branch block and anterior infarction.

short distance so that the electrode could be connected to the appropriate lead wire. The precordial points explored were arranged along a broken line running across the precordium from right to left, and were approximately 2 cm. apart. The exploring electrode used in taking both the precordial and the direct leads was paired with a central terminal connected through resistances of 5,000 ohms to electrodes on the two forelegs and on the right hind leg. Leads taken in this way are referred to as "unipolar leads."

The unipolar precordial curves obtained in uncomplicated canine bundle branch block are strikingly similar to those that represent human bundle branch block, apart from the length of the QRS interval, which is considerably shorter in the dog than in man. In left branch block there are no other easily detectable differences. In leads from the right side of the precordium the QRS complex consists of a small initial R component, followed by a deep, broad S deflection. In leads from the left side of the precordium it is monophasic, and is represented by a broad-topped, slurred, notched, or bifid R wave (Fig. 2, Dog 64).

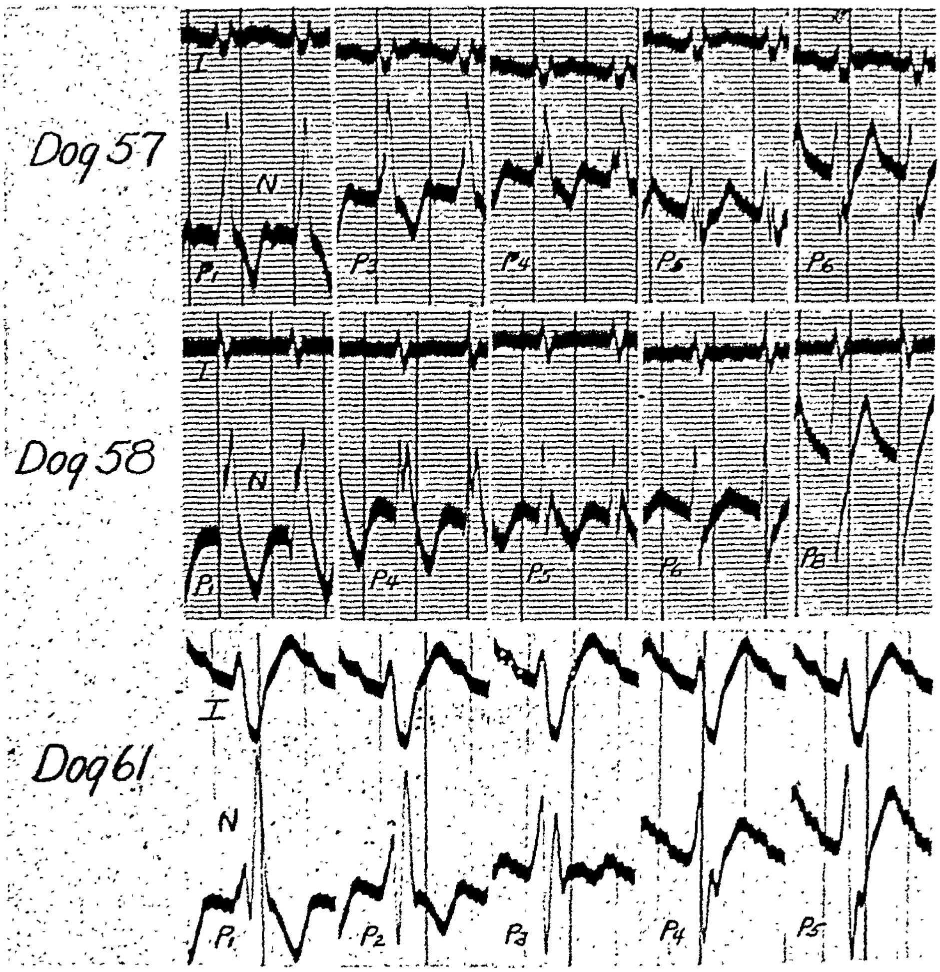

Fig. 3.—Unipolar precordial leads from three dogs with right bundle branch block.

In right bundle branch block the leads from the right side of the precordium display a large R or R′ deflection which reaches its apex late in the QRS interval. In some instances this deflection is preceded by an initial downward movement, or Q wave (Fig. 3, Dogs 57 and 58), in which case its ascending limb is usually slurred or notched. In other instances (Fig. 3, Dog 61) it is preceded by a small initial R component, followed by a conspicuous dip, and notching of its upstroke is absent or less conspicuous. As the exploring electrode is shifted to

the left this initial R rapidly increases in height and is transformed into a slender, tall, upward deflection which reaches its apex early in the QRS interval. At the same time, the downward movement which follows it increases in depth, and the late secondary R′ component rapidly diminishes in size until it is represented by a notch on a deep, broad S wave. Precordial electrocardiograms of this second type are very much more common in human right branch block than those of the first type. In leads from the left side of the precordium the QRS complex always has essentially the same form, and consists of a narrow R deflection, sometimes preceded by a small Q, and a broad, slurred, or notched S wave. The voltage of the slender R is usually smaller in comparison with that of the broad S in the curves of the dog than in those of man.

When right branch block is complicated by anterior infarction (Fig. 4), leads from the right side of the precordium display a tall, late R wave, preceded by a deep Q deflection. As the exploring electrode is shifted to the left the R wave rapidly diminishes in size, and disappears or is submerged below the isoelectric level. In leads from the left side of the precordium the early, slender R wave which is present when there is no infarction is absent, submerged, or greatly reduced in height. In other words, the characteristic changes in the QRS complex consist in the development of large Q or QS deflections in leads from points overlying the infarct, and large Q waves, followed by late R waves, in leads from the right side of the precordium. In one of our experiments (Dog 66) the QRS complex of the lead taken farthest to the right (P_{10}, Fig. 4) showed no changes suggesting infarction. When left bundle branch block is present, anterior infarction gives rise to no characteristic modification of the QRS complex in precordial leads (Fig. 2, Dogs 68 and 70).

Intelligent interpretation of the ventricular complexes of unipolar precordial leads must be based upon the relations between the components of these complexes and the corresponding deflections of unipolar leads from the anterior surface of the exposed heart. In the animals with bundle branch block but no infarction, there was a very close resemblance between the ventricular complexes of the leads from the right side of the precordium and the ventricular complexes of the leads from the exposed surface of the right ventricle, and likewise between the complexes of the leads from the left side of the precordium and those of the leads from the exposed surface of the left ventricle. Curves depicting these relations in right branch block without infarction (Dog 58) and in left branch block without infarction (Dog 64) have recently been published in a general article on the precordial electrocardiogram.[2] We shall, therefore, confine the present discussion to experiments in which bundle branch block was complicated by infarction. In order to conserve space and to avoid needless repetition, comments and discussion necessary to the understanding and interpreta-

tion of the observations made in the experiments described here in detail have not been relegated to a separate section, but are interspersed with the presentation of the relevant data.

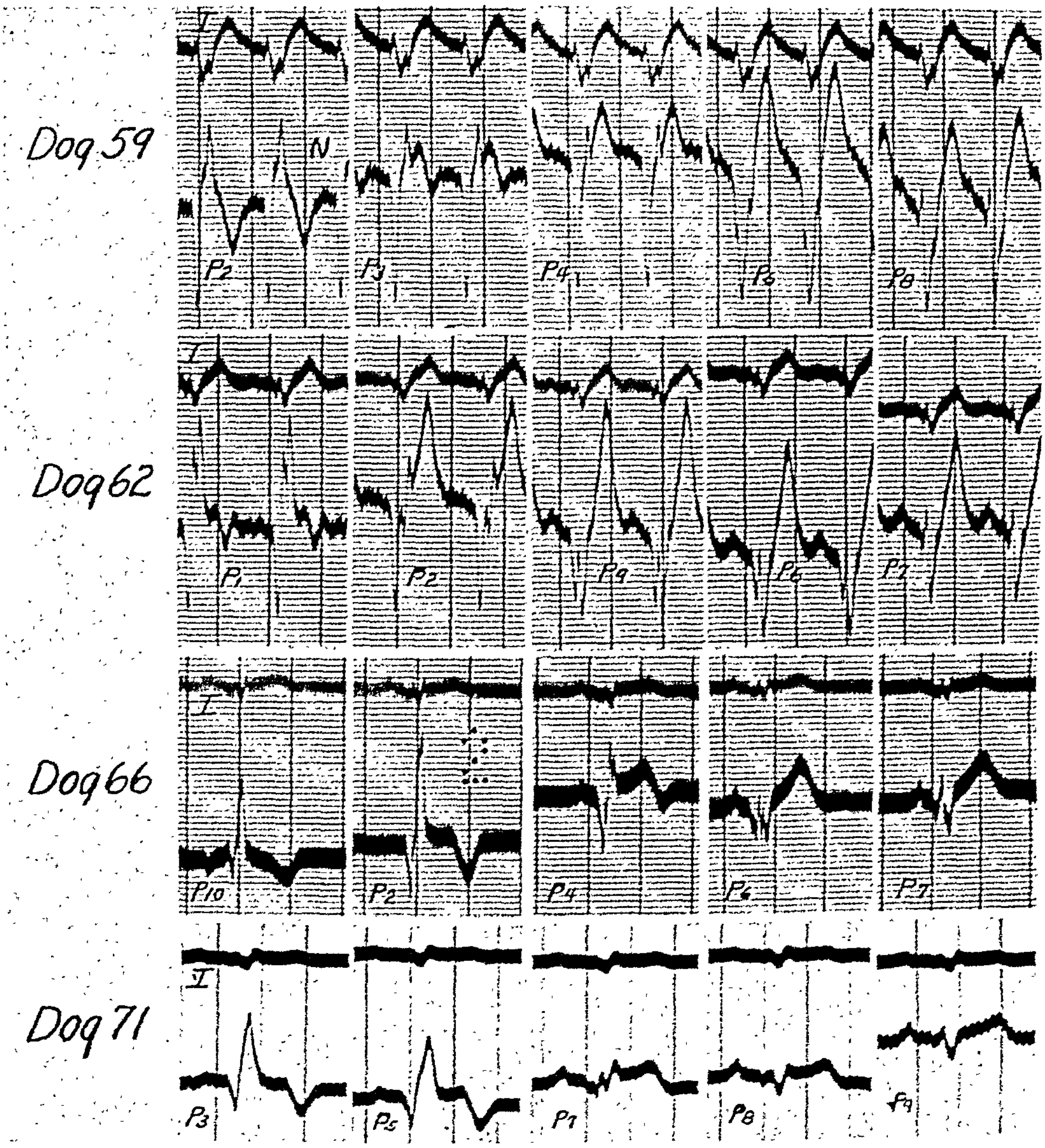

Fig. 4.—Unipolar precordial leads from four dogs with right bundle branch block and anterior myocardial infarction.

Dog 66.—The locations of the points on the epicardial surface explored in this experiment are shown on the outline drawing of the heart reproduced in Fig. 5. The points indicated by numbers not followed by a letter were studied with a soft-tipped electrode consisting of a small glass tube connected to a short length of soft rubber tubing cut on a bias at its lower end. The glass tube was stoppered with salted kaolin, and filled with 10 per cent copper chloride solution in which a long coil of copper wire was immersed. The short rubber extension was packed with cotton wool saturated with isotonic saline. When this electrode

was pressed lightly against the epicardium, no injury or only minimal injury to the underlying muscle resulted. The points marked by numbers followed by the letter *s* were explored with the sharp electrode used in taking precordial leads. This electrode was employed to distinguish dead from living muscle. When it was brought into contact with the former there were no injury effects in the curve obtained, but the latter yielded prominent RS-T displacement or completely monophasic ventricular complexes. The points designated by numbers followed by the letter *c* are those at which the sharp electrode was thrust *through* the ventricular wall in order to record the potential variations of the ventricular cavity. The first of the precordial curves reproduced (P_{10} of Fig. 6) was obtained from a point approximately 4.5 cm. to the right of the midsternal line. The ventricular complexes which it displays are

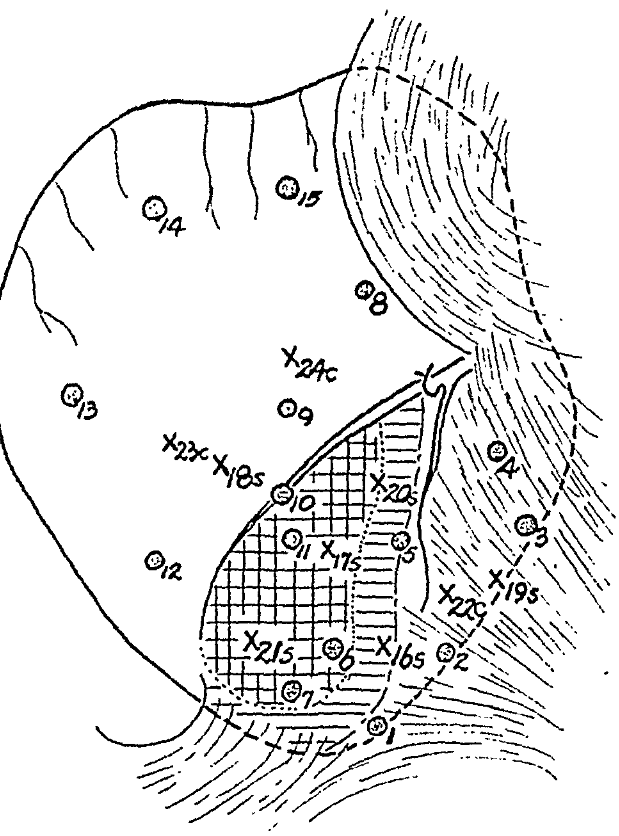

Fig. 5.—Dog 66. Outline drawing of anterior surface of exposed heart. Points explored with soft-tipped electrode indicated by stippled circles. Points explored with sharp electrode indicated by *X*; records taken from the surface are lettered *s*, and from the ventricular cavity are lettered *c*.

strikingly similar in outline to those of the direct leads from points *8, 12, 13, 14,* and *15,* which were all on the right ventricle. Since the deflections of all these leads are similar, only one, that from point *14,* is reproduced (Fig. 6). In these tracings the first QRS component is a small R wave, followed by a dip which reaches or barely crosses the isoelectric level. The second component is a tall R′ deflection which reaches its apex late in the QRS interval and displays a shoulder on its ascending limb. In right bundle branch block the muscle of the free wall of the right ventricle is not activated until late in the QRS

interval. During the earlier phases of this interval it contains no boundary between active and resting muscle and produces no electromotive forces. So long as this is the case, the potential of its outer surface is practically identical with that of the neighboring part of the ventricular cavity. It is not surprising, therefore, that in the tracings obtained from the ventricular cavity by thrusting a sharp electrode through the wall of the right ventricle at points *23c* and *24c* (Fig. 6), the earliest phases of the QRS complex are similar to the corresponding phases of the QRS complexes of the epicardial leads. The small, early R wave of these leads is faithfully reproduced in the internal leads.

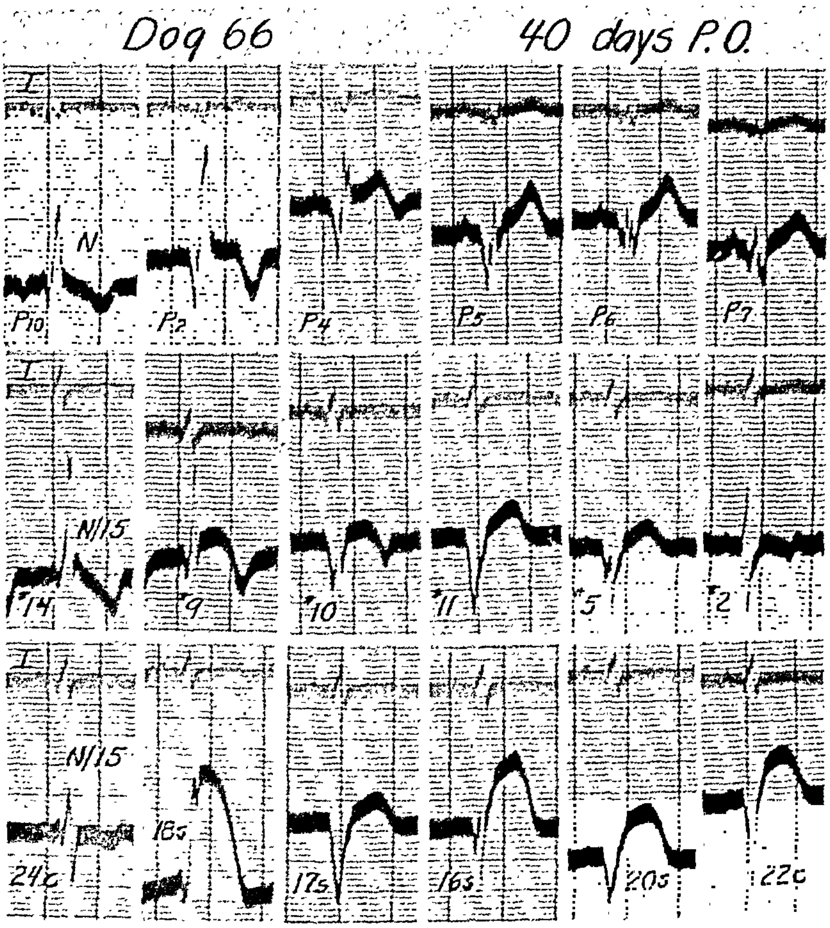

Fig. 6.—Dog 66. Right bundle branch block and anterior infarction. Upper row—unipolar precordial leads. Middle row—epicardial leads obtained with soft-tipped electrode. Lower row—epicardial and cavity leads obtained with sharp electrode.

The second R peak of the latter, which represents the maximum positivity attained by the ventricular cavity, evidently corresponds to the shoulder or thickening of the ascending limb of the late R′ deflection of the external leads. During the latter part of the QRS interval the epicardial surface is positive and the ventricular cavity negative, indicating that there is then a large electromotive force in the right ventricular wall. This force is responsible for that part of the late

R′ wave of the epicardial leads which follows the shoulder on its ascending limb.

It will be noted that the ventricular complexes of the lead from point *18s*, in which there is almost complete fusion of QRS and T due to the injury to the subepicardial muscle induced by the sharp electrode, do not differ, as regards those QRS components which precede the peak of the late R′ deflection, from the complexes obtained when a soft electrode was used. It has been pointed out in a previous publication[3] that injury to the subepicardial muscle can have no effect upon the form of the ventricular complex up to the instant at which the excitatory process arrives at the injured region. Since the subepicardial muscle of the right ventricle is not activated in right bundle branch block until the peak of R′ is inscribed, injury to this muscle has no effect on the earlier phases of the QRS complex.

The ventricular complexes of the direct leads from points *9* and *10* (Fig. 6) display a slender R or R′ deflection which reaches its apex late in the QRS interval and is preceded by a conspicuous downward movement. The RS-T segment is convex upward and the end of the T wave sharply inverted. The QRS complexes of the lead from point *9* begin with a small initial R, which is missing in the lead from point *10*. Both of these points were close to the interventricular sulcus, but their exact relation to the anterior attachment of the septum is not known. It is often difficult to interpret the deflections of leads of this kind because of uncertainty as to whether the recorded potential variations of the epicardial surface were more closely related to those of the right or to those of the left ventricular cavity. In the case of the lead from point *10*, it appears probable that the early phases of the QRS complex were determined by the potential variations of the cavity of the left ventricle; in the case of the lead from point *9*, the corresponding phases of QRS are apparently due in part to the potential variations of the cavity of the right ventricle. The ventricular complexes of these leads display many of the features often seen in leads from the marginal parts of an infarct which involves the left ventricular wall and is more extensive on its endocardial than on its epicardial side.

Unipolar epicardial leads from transmural infarcts that contain no appreciable amount of muscle capable of responding to the excitatory process yield ventricular complexes almost identical with those of leads from the adjacent part of the ventricular cavity. It will be noted that the ventricular complexes of the lead from point *11* are similar to those of lead *22c*, which represent the potential variations of the cavity of the left ventricle, and that the ventricular complexes of lead *17s*, in which a sharp exploring electrode was employed, are of the same kind. Since the last shows no RS-T displacement, it is evident that the muscle in the neighborhood of points *11* and *17s* was dead, or at least not responding to the cardiac impulse. The leads from points *6* and *7* and

the lead from point *21s* gave complexes practically identical in outline with those of the leads from points *11* and *17s*.

Unipolar epicardial leads from parts of left ventricular infarcts that contain appreciable amounts of muscle which responds to the cardiac impulse and lies in the outer layers of the ventricular wall yield QRS complexes characterized by large QS deflections notched by submerged R waves, or by abnormally large Q components followed by R waves of subnormal voltage. Infarction of the outer layers of muscle without involvement of the inner layers should theoretically reduce the size of the R component without producing abnormal Q waves, but this appears to be rare or nonexistent. In the present instance, notched QS deflections occurred in the lead from point *5*. The leads from points *16s* and *20s* show definite RS-T displacement, indicating the presence of living muscle. In the former the small R component is preceded by a broad Q deflection, which suggests that the subendocardial muscle was involved. Points *5*, *16s*, and *20s* evidently lie near the left margin of the infarct. The ventricular complexes of precordial leads P_1, P_5, and P_6 were evidently dominated by the potential variations of the infarcted region; they show many of the features of the ventricular complexes of the direct leads from points *5* and *11*.

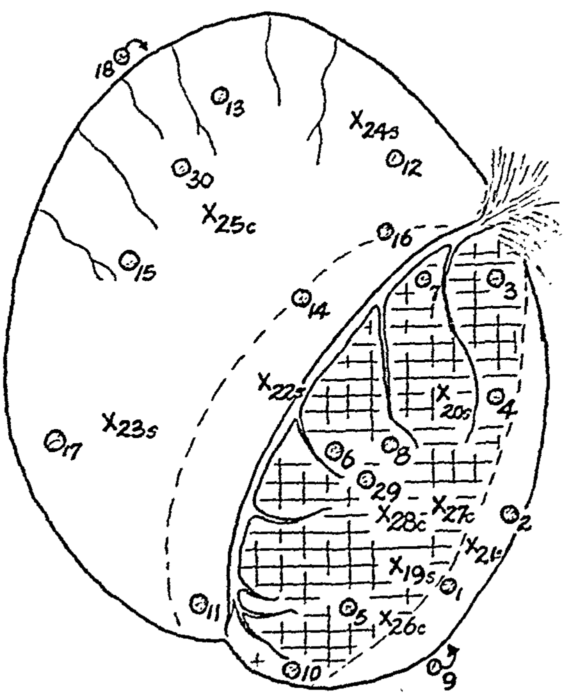

Fig. 7.—Dog. 71. Outline drawing of anterior surface of exposed heart. Symbols as in Fig. 5.

The direct leads from points *1*, *2* (see Fig. 6), *3*, and *4*, which were still farther to the left and in a zone supplied by a branch of the anterior descending artery which came off above the ligature, present ventricular complexes of the normal form. The lead from point *19s* shows conspicuous RS-T displacement, indicating that the muscle in

this zone was responding. All of these points evidently lie to the left of the infarcted region. The ventricular complexes of precordial lead P_7 apparently represent a mixture of the potential variations at the surface of the infarct and those at the surface of the uninvolved wall to the left of it.

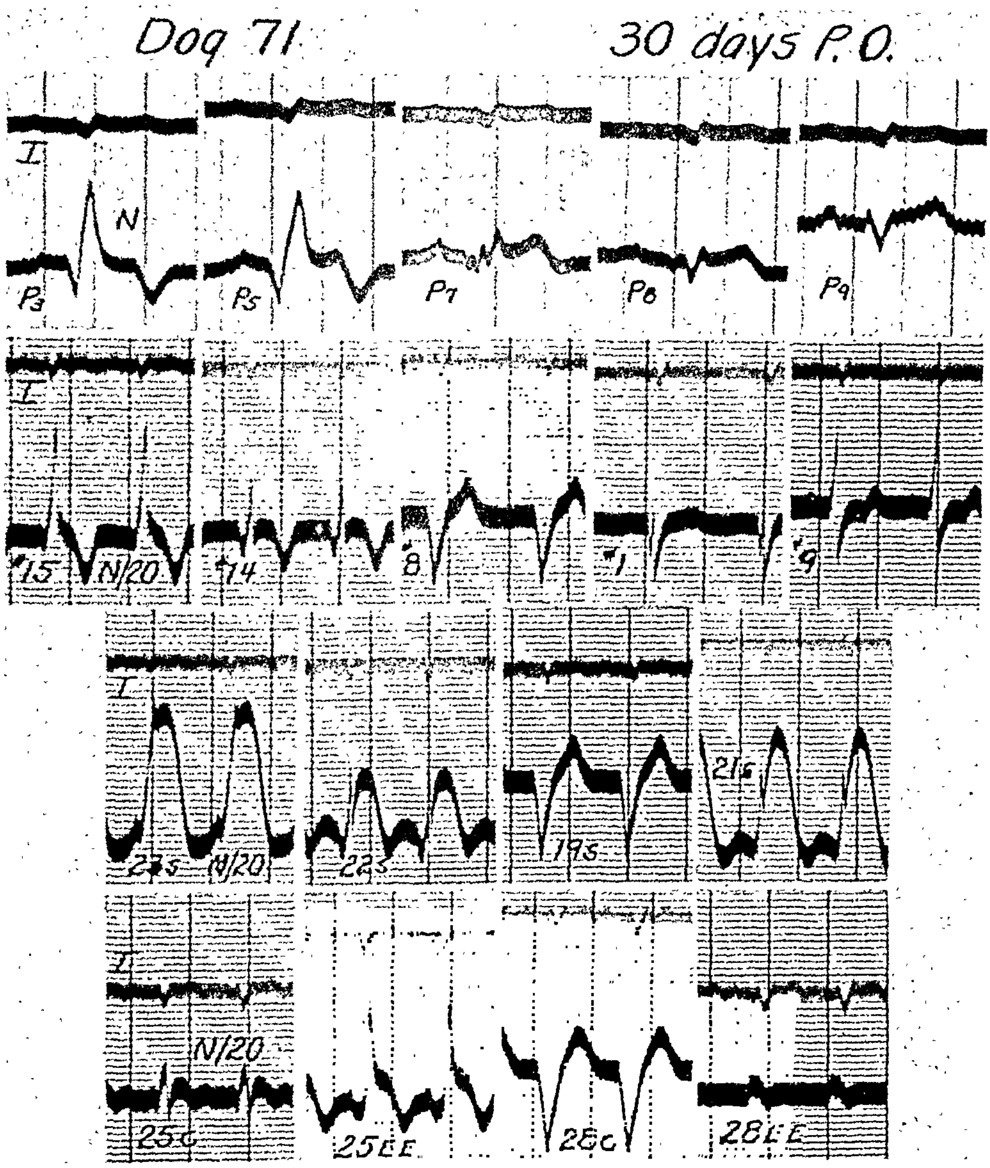

Fig. 8.—Dog 71. Right bundle branch block and anterior infarction. First row—unipolar precordial leads. Second row—epicardial leads obtained with soft-tipped electrode. Third row—epicardial leads obtained with sharp electrode. Fourth row—leads from ventricular cavities and transmural leads (marked *EE*).

Dog 71.—The locations of the epicardial points explored in this experiment are indicated in Fig. 7, and characteristic examples of the curves obtained are reproduced in Fig. 8. The ventricular complexes of the leads from points *11, 13, 17,* and *18* are similar in every respect to those of the lead from point *15* (Fig. 8). All of these points were on the free wall of the right ventricle. In the leads from points *12, 14,* and *16,* the QRS complex consists of a prominent Q wave, followed by a late R deflection which is very small in the lead from the last of these points; the T wave is sharply inverted. Points *14* and *16* were close

to the interventricular sulcus, and it is possible that point *12* was much less distant from it than is indicated in Fig. 7. The curves obtained with the sharp electrode at points *22s, 23s,* and *24s* show pronounced RS-T displacement; in the first the earliest phases of the QRS complex are like those of the lead from point *14,* and in the others they are like those of the lead from point *15* and like those of the lead from the cavity of the right ventricle at point *25c.* It will be observed that the potential variations of the different parts of the epicardial surface and of the cavity of the right ventricle in this experiment were strikingly similar to those recorded in the case of Dog 66.

In the leads from points *3, 4, 5, 6, 7, 8,* and *10,* the ventricular complexes consist of large, unnotched QS deflections, followed by positive T waves, and do not differ from those of the leads from the left ventricular cavity at points *27c* and *28c,* or from those of the leads from points *19s* and *20s.* The absence of RS-T displacement in these last two leads indicates that the muscle in contact with the sharp electrode was not responding to the cardiac impulse. The leads from points *1* and *2* present notched QS deflections, and the lead from point *21s* shows conspicuous RS-T displacement. These points were evidently close to the left margin of the infarct. In the lead from point *9,* the ventricular complexes are of the normal form. In this experiment transmural leads were taken in order to measure the variations in the voltage across the ventricular walls during the QRS interval. In these leads a sharp electrode thrust through the wall into the ventricular cavity was paired with a soft electrode on the epicardial surface. The galvanometer connections were made in such a way that relative positivity of the epicardial electrode produced an upward deflection in the finished record. In the lead marked *25 EE,* the soft electrode was on the free wall of the right ventricle at point *30,* and the sharp electrode was in the right ventricular cavity near point *25c.* The QRS complexes of this lead begin with a broad, shallow Q deflection, indicating slight relative negativity of the external surface. Late in the QRS interval there is a tall, sharp R deflection due to activation of the muscle between the two electrodes which made the epicardial surface strongly positive with respect to the ventricular cavity. The RS-T displacement is upward, and probably represents injury due to the pressure exerted by the outer electrode. The lead marked *28EE* was obtained by pairing a soft electrode at point *29* on the outer surface of the infarct with an internal electrode thrust through the ventricular wall at point *28c.* In this case the QRS deflections are very small. Since the infarcted muscle was not responding to the cardiac impulse, this part of the ventricular wall developed no electromotive force between its inner and outer surfaces. The small potential difference recorded is ascribed to electromotive forces generated at a considerable distance from the two electrodes and bearing nearly the same spatial relation to both of them.

The precordial leads in this experiment are clearly diagnostic of right branch block complicated by anterior infarction. There are abnormally large Q waves, followed by late R deflections in the leads from the right side of the precordium, and in the leads from the left side of the precordium the early R component ordinarily present in uncomplicated right branch block is absent, submerged, or abnormally small. It is also clear that the potential variations of the precordial points and the potential variations of the nearest parts of the ventricular surface were closely related. The resemblance between the precordial curves and the ventricular complexes of the direct leads is, however, somewhat less striking than in the case of Dog 66. Since large QS deflections occurred in the direct leads from a large part of the anterior surface of the left ventricle, it is surprising that they were not more faithfully reproduced in the leads from the left side of the precordium. If the precordium had been more completely explored, QS deflections larger than those present in precordial lead P_8 might have been obtained.

Dog 59.—The locations of the epicardial points investigated in this experiment are indicated in Fig. 9, and characteristic examples of the curves obtained are reproduced in Fig. 10. The leads from points *3*, *4*, *8*, and *19* on the free wall of the right ventricle display a late R wave, preceded by small preliminary deflections consisting of an initial downward movement followed by a positive deflection of about the same size. This second preliminary deflection notches the ascending limb of R. Similar preliminary deflections are present in the leads from points *13s* and *25s*, which were taken with the sharp electrode, but in the last the downward movement is preceded by a small positive peak. In the lead from the ventricular cavity at point *24c* this positive peak is well developed, but it is not followed by a conspicuous depression. The principal R wave of this internal lead corresponds in time to the notch or shoulder on the upstroke of the R wave of the epicardial leads. The difference between the earliest potential variations of the right ventricular cavity and those of the epicardial surface of the free wall of the right ventricle was not, therefore, as great as the first glance at the tracings suggests.

In the leads from points *2*, *12s*, *17s*, and *21s*, all close to the interventricular sulcus, the ventricular complex consists of a conspicuously notched QS deflection of moderate depth, followed by a positive T wave. Since the sharp electrode produced no upward RS-T displacement in the last three of these leads, it is apparent that most of the muscle in this zone was dead and that the infarct extended across the interventricular sulcus.

In the leads from points *1*, *7*, and *18*, the QRS complex consists of a deep, notched or slurred QS deflection. At points *10s*, *14s*, and *23s*, the sharp electrode yielded deep Q or QS deflections, followed by moderate upward displacement of the RS-T junction, indicating that some

of the subepicardial muscle, but not all of the subendocardial muscle at these points, was responding to the cardiac impulse. The leads from points *5, 6, 9, 11s,* and *20s* indicate that the corresponding parts of the ventricular wall were normal. At point *22s* the sharp electrode yielded a curve which shows no upward RS-T displacement, and in which the QRS complex is unnotched and similar to that of the lead from the cavity of the left ventricle near point *23c,* indicating that in this region the infarct was transmural.

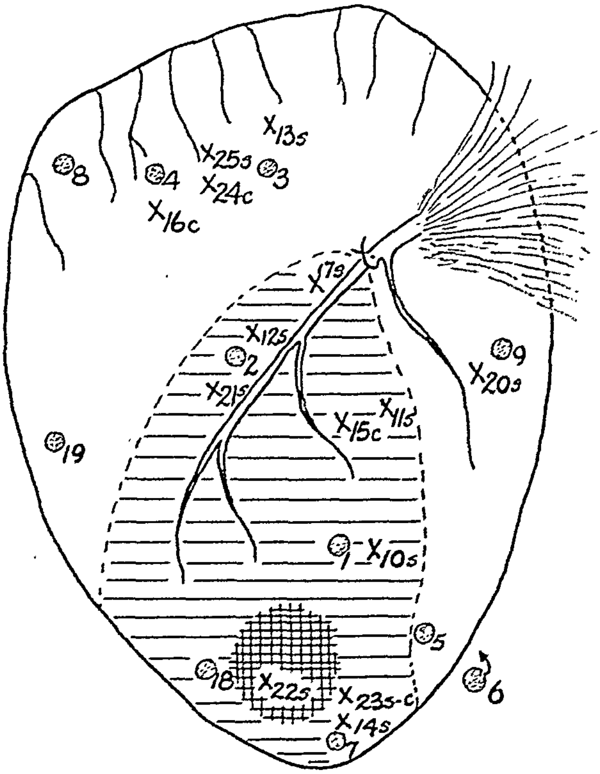

Fig. 9.—Dog 59. Outline drawing of anterior surface of exposed heart. Symbols as in Fig. 5.

There is a close relation between the form of the ventricular complexes of the leads from the left side of the precordium and those of the direct leads from the epicardial surface of the left ventricle. In the leads from the right side of the precordium the initial Q deflection is much larger in comparison with the late R wave than in the two experiments previously described (Dogs 66 and 71). As regards the presence of these large Q components, the ventricular complexes of these leads are unlike those of the direct leads from the epicardial surface of the free wall of the right ventricle. The same phenomenon is seen in the semidirect leads (*SD* in Fig. 10) which were taken from a pad of gauze soaked in isotonic saline solution and laid upon the exposed heart. This pad was approximately 1 cm. thick, and the exploring electrode was moved across it step by step in a base-apex direction, so that the earliest leads (*1* and *2*) were from parts of the pad lying on the right ventricle. The ventricular complexes of these leads resemble those of

the corresponding precordial leads in general contour. It is apparent that in this experiment the potential variations of the surface of the infarct were unusually well transmitted to the right side of the precordium and to the right side of the gauze pad. The reason may lie in the extension of the infarct to the right of the interventricular sulcus. The same phenomenon occurred in the case of Dog 62, but in this instance the animal died prematurely, so that a satisfactory number of direct leads could not be taken. In this experiment, also, there was spotty infarction of the part of the right ventricular wall adjacent to the sep-

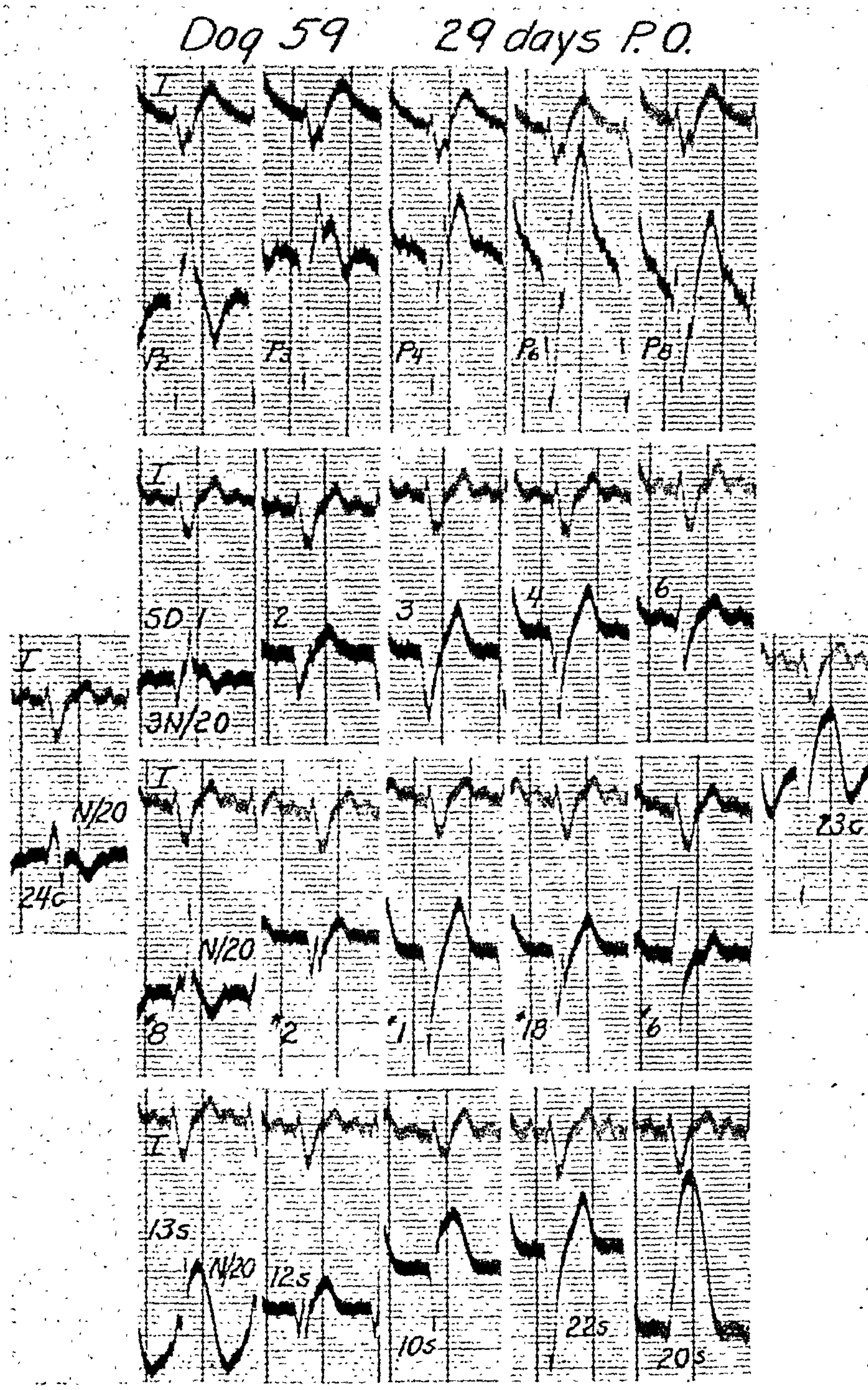

Fig. 10.—Dog 59. Right bundle branch block and anterior infarction. First row—unipolar precordial leads. Second row—semidirect leads from saline soaked gauze pad laid upon exposed heart. Third row—epicardial leads with soft-tipped electrode. Fourth row—epicardial leads with sharp electrode. Tracings labeled *24c* and *23c* are leads from the right and left ventricular cavities, respectively.

tum. It should be noted that, during the earliest parts of the QRS interval, the potential variations of the surface of the infarct were much larger than those of the right ventricular surface, whereas later in this interval this situation no longer existed. This explains why the potential variations of the right side of the precordium were at first like those of the infarcted region, and later like those of the anterior surface of the right ventricle.

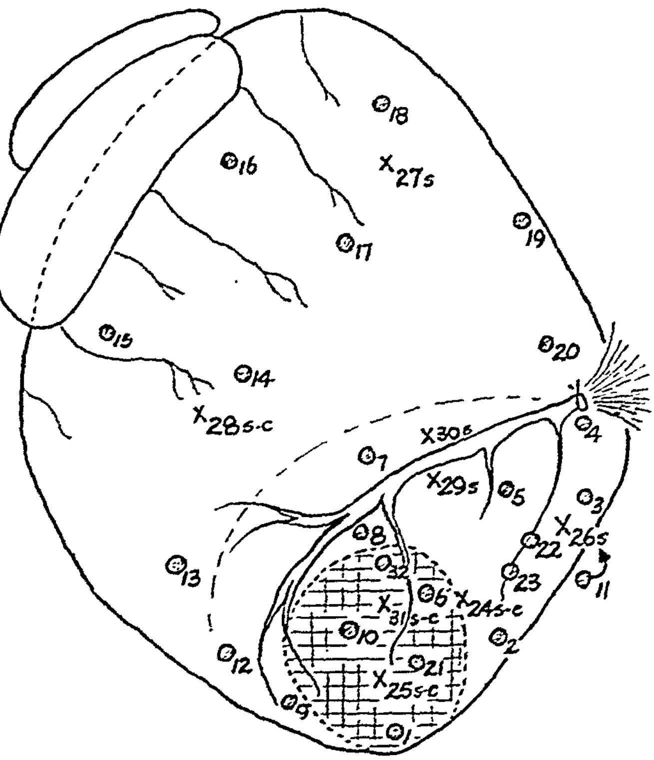

Fig. 11.—Dog 70. Outline drawing of anterior surface of exposed heart. Symbols as in Fig. 5.

Dog 70.—The locations of the epicardial points explored in this experiment are shown in Fig. 11, and some of the tracings obtained are reproduced in Fig. 12. In the leads from the free wall of the right ventricle at points *13, 14, 15, 16, 18,* and *19,* the QRS complex consists of a slender initial R deflection, followed by a deep, broad, and slurred S wave. The T wave is upright. The ventricular complex is of the same form in the leads from points *7, 12,* and *20,* except that in the last there is a mere trace of the initial R wave, and also in the leads from points *4, 5, 8,* and *9,* which were equally close to the anterior descending artery, but on the opposite side of it. In the dog it is the rule that the time of activation of points just below this artery is not much affected by section of either the right or left bundle branch. At points *27s, 28s, 29s,* and *30s,* the sharp electrode induced pronounced upward RS-T displacement.

In the lead from point *2* the QRS complex consists of a tall, late R wave which displays conspicuous slurring of the first part of its ascend-

ing limb. This limb is notched near its onset by a small summit. The T waves are inverted. Ventricular complexes of essentially the same kind are present in the leads from points *11*, *22*, and *23*. In the lead from point *3* the peak of the R wave is earlier, but in this lead, also, this deflection is preceded by a small summit. There are a large S and a

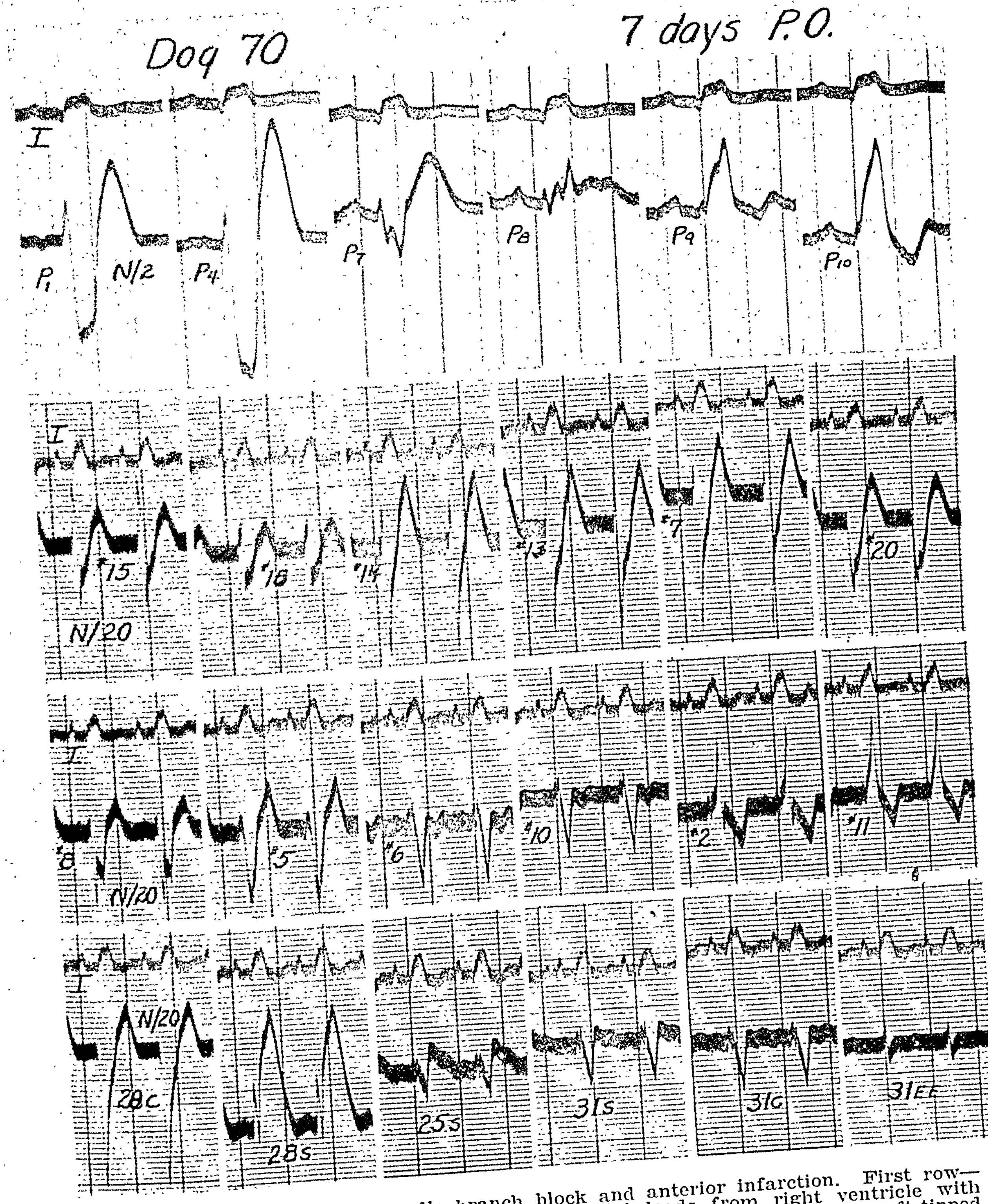

Fig. 12.—Dog 70. Left bundle branch block and anterior infarction. First row—unipolar precordial leads. Second row—epicardial leads from right ventricle with soft-tipped electrode. Third row—epicardial leads from left ventricle with soft-tipped electrode. Fourth row—epicardial and cavity leads with sharp electrode. Transmural lead labeled *EE*.

positive T wave. The sharp electrode produced a large upward displacement of the RS-T junction in the lead from point *26s*.

In the leads from points *1, 6, 10,* and *21,* the ventricular complexes are of essentially the same form as in the lead from the ventricular cavity near point *24c*. The QRS deflections consist of two sharp, but very low, summits, followed by a deep S deflection, and the T wave is diphasic or inverted. The sharp electrode yielded moderate upward RS-T displacement at point *24s,* slight displacement at point *25s,* and very slight displacement at point *31s*. In all of these leads the initial QRS deflections are similar to those of the lead from the ventricular cavity. It is apparent that a considerable part of the ventricular wall in this region was infarcted.

A transmural lead from the ventricular cavity near point *31c* to the epicardial surface at point *32* (marked *31EE* in Fig. 12) shows very small deflections, indicating that the ventricular wall in this neighborhood was producing no appreciable electromotive force and was not responding to the cardiac impulse. It should be pointed out that in the leads from the infarcted region (points *1, 6, 10,* and *21*) the large downstroke which begins at the peak of R is not nearly as steep as it is in the leads from uninjured parts of the ventricular walls. The absence of a very abrupt downstroke or true intrinsic deflection distinguishes the QRS complex of these leads from those of all the other leads taken with the soft electrode, with the possible exception of the lead from point *5* (see Fig. 12).

The ventricular complexes of the leads from the right side of the precordium (P_1 to P_7, inclusive) are strikingly similar in general outline to those of the direct leads from the free wall of the right ventricle and the zones on either side of the anterior descending coronary artery. The ventricular complexes of the leads from the left side of the precordium (P_9 and P_{10}) resemble those of the direct leads from the uninfarcted anterolateral wall of the left ventricle. None of the precordial leads displays ventricular complexes like those of the direct leads from the surface of the infarct. The reason probably lies in the relatively small size of the region within which a large part of the ventricular muscle was killed. But even if this region had been much larger, and the potential variations over its surface had been more faithfully transmitted to the precordium, it is unlikely that modifications of the precordial curves diagnostic of infarction would have resulted. As has been clearly shown, the potential variations at the epicardial surface of a transmural infarct are always practically identical with those of the adjacent parts of the ventricular cavity. When the left branch of the His bundle conducts normally, the cavity of the left ventricle is negative throughout the QRS interval, and leads from the surface of trans-

mural left ventricular infarcts yield deep QS deflections which clearly indicate the nature of the lesion. If the infarct is anterior and not too small, similar deflections occur in suitable precordial leads. When left branch block is present, however, the cavity of the left ventricle is positive at the beginning of systole because of the electromotive force generated by the spread of the cardiac impulse through the septum from right to left. In this case, leads from the outer surface of a transmural infarct of the left ventricular wall display QRS complexes that consist of an R deflection of variable size, followed by an S wave of like or greater voltage. Such deflections in precordial leads are not sufficiently distinctive to have much diagnostic value. If they occur in leads from the extreme left side of the precordium, which ordinarily yield QRS complexes consisting of a single component, a broad, slurred, notched, or bifid R wave, they may justifiably lead to the suspicion that an infarct is present, but cannot furnish reliable evidence of the existence of such a lesion. The recognition of infarction of the free wall of the left ventricle in the presence of left bundle branch block on the basis of modifications of the QRS complex is, therefore, extremely difficult.

SUMMARY

In dogs, myocardial infarcts induced by ligating the anterior descending coronary artery in its middle third do not usually modify the QRS complexes of the standard limb leads in a characteristic manner when bundle branch block is present.

When such infarcts are complicated by right bundle branch block, the QRS complexes of unipolar leads from the right side of the precordium display a large, initial Q deflection, followed by an R wave which attains its summit late in the long QRS interval. The first component is due to potential variations transmitted from the epicardial surface of the infarcted region, and the second to potential variations transmitted from the epicardial surface of the free wall of the right ventricle. Leads from that part of the precordium overlying the infarct present large, broad QS deflections, often conspicuously slurred or notched.

When left branch block is present, infarction of the kind in question does not give rise to characteristic changes in the QRS complexes of the precordial leads because the potential of the left ventricular cavity and, therefore, of the epicardial surface of the infarcted region is positive during the earliest part of the QRS interval. In direct leads from the epicardial surface of the infarct, the QRS complex consists of an initial R deflection of variable size, followed by an S component of like or greater voltage. In the case of very large lesions, QRS complexes of this kind probably occur in leads from precordial points overlying the part of the left ventricular wall which is affected, but cannot be considered reliable evidence of infarction.

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CORONARY OCCLUSION, CORONARY INSUFFICIENCY, AND ANGINA PECTORIS

A Clinical and Post-Mortem Study

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THE frequency of disease of the coronary arteries[1, 2] has lent great impetus in recent years to the study of this disease, both clinically and pathologically.[3-5] It is now known to be the most important disease of all, considering all age groups. In large part this is due to the increase in the span of life,[1] enabling many more persons to reach the age at which coronary artery disease is prevalent. The subject is of critical importance today, when a large army is being formed, for it has been shown that coronary artery disease is common among military personnel over the age of 40 years.[6] It is, therefore, essential that correct terminology be used in discussing coronary disease, but considerable confusion exists at the present time with respect to the use of the terms "coronary occlusion" and "coronary insufficiency."

Coronary artery occlusion means sudden, complete obstruction of a coronary artery. The symptoms and signs associated with the attack include severe and prolonged substernal pain, shock, impairment of the first heart sound, gallop rhythm, occasionally a pericardial rub, a fall in blood pressure, fever, leucocytosis, and a rapid sedimentation rate. Acute coronary insufficiency indicates necrosis or infarction of the myocardium without complete closure of a coronary artery. This concept of acute coronary insufficiency has been firmly established as a specific entity by the work of many authors, both in Germany[7-11] and in this country.[6, 12-16] It has been demonstrated conclusively that pain and necrosis or infarction of the myocardium may be produced by severe or prolonged diminution in coronary flow in the absence of coronary occlusion.

Some writers[17, 18] have been prompted to discard the term "coronary occlusion" on the assumption that it is impossible clinically to differentiate coronary occlusion with infarction from coronary insufficiency with necrosis or infarction of the heart muscle. They thus relegate the term "coronary occlusion" to the post-mortem room. We do not agree with this point of view, for, in our experience, coronary occlusion with infarction presents characteristic clinical and electrocardiographic changes which are almost always distinguishable from those produced

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Received for publication June 1, 1943.
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TABLE 1

DIFFERENTIATION OF ANGINA PECTORIS, CORONARY INSUFFICIENCY, AND CORONARY OCCLUSION

	ANGINA PECTORIS	ACUTE CORONARY INSUFFICIENCY	CORONARY OCCLUSION
PHYSIOLOGY	Ischemia, transitory (inadequate coronary circulation)	Ischemia, severe or prolonged (inadequate coronary circulation)	Total cessation of coronary flow in obstructed artery
PATHOLOGY	1. Coronary arteries: sclerosis and narrowing 2. Myocardium: no acute changes	Variable degree of sclerosis or normal Necrosis: small, diffuse areas, subendocardial, papillary muscle No pericarditis No mural thrombosis	Sclerosis. Occlusion by thrombus or intimal hemorrhage Infarction—large, confluent, endo-, myo-, and pericardial Pericarditis common Mural thrombosis with embolization common
PREDISPOSING FACTORS	Coronary sclerosis Hypertension Aortic stenosis and insufficiency Graves' disease Anemia Syphilitic ostial stenosis	Coronary sclerosis Hypertension Aortic stenosis Cardiac enlargement Anemia Syphilitic ostial stenosis	Coronary sclerosis Hypertension
PRECIPITATING FACTORS	Effort Emotion Cold Eating Trauma Reflex from other viscera Tobacco Insulin Adrenalin	1. Similar to angina pectoris 2. Acute conditions with anoxemia Hemorrhage Shock or fall in blood pressure Sudden rise in blood pressure Tachycardia Heart failure Infections Trauma Operation, anesthesia	None Operation?
PAIN	Temporary Relieved by nitroglycerin	Variable, often absent	Prolonged Not relieved by nitroglycerin
[illegible]			
1. Shock	None	May be present	Common
2. Blood pressure	No change or rise	Falls	Falls
3. Heart sounds	No change	May be poor	Embryocardia, gallop, pericardial rub
4. [illegible]	None	Occasional	Common
5. [illegible]	None	May be present	Common
6. [illegible]	Absent	Frequently absent	Present
7. Sedimentation rate	Normal	Frequently normal	Abnormal
ECG	Usually no change Evanescent RS-T depressions	RS-T depressions and T-wave changes for several days or weeks No Q waves or RS-T elevation	RS-T elevation Q waves Leads I and III reciprocal Progressive pattern, often permanent
DURATION OF INCAPACITY	Minutes to few hours	Several hours or weeks	Prolonged
PROGNOSIS	Good	Usually full recovery Occasionally fatal Often depends upon precipitating factor	Usually permanent symptoms Often fatal

by infarction caused by coronary insufficiency.[13-16] Although both conditions occasionally result in similar clinical entities, coronary occlusion usually presents a well-defined syndrome which is readily distinguished from coronary insufficiency, and both conditions differ in their causal relationship to severe exertion and trauma. It is thus obvious that a correct terminology of coronary disease is essential, and that it is important to distinguish coronary occlusion clearly from coronary insufficiency.

A major difference between coronary occlusion and coronary insufficiency is in the mode of onset (Table I). The start of coronary oc-

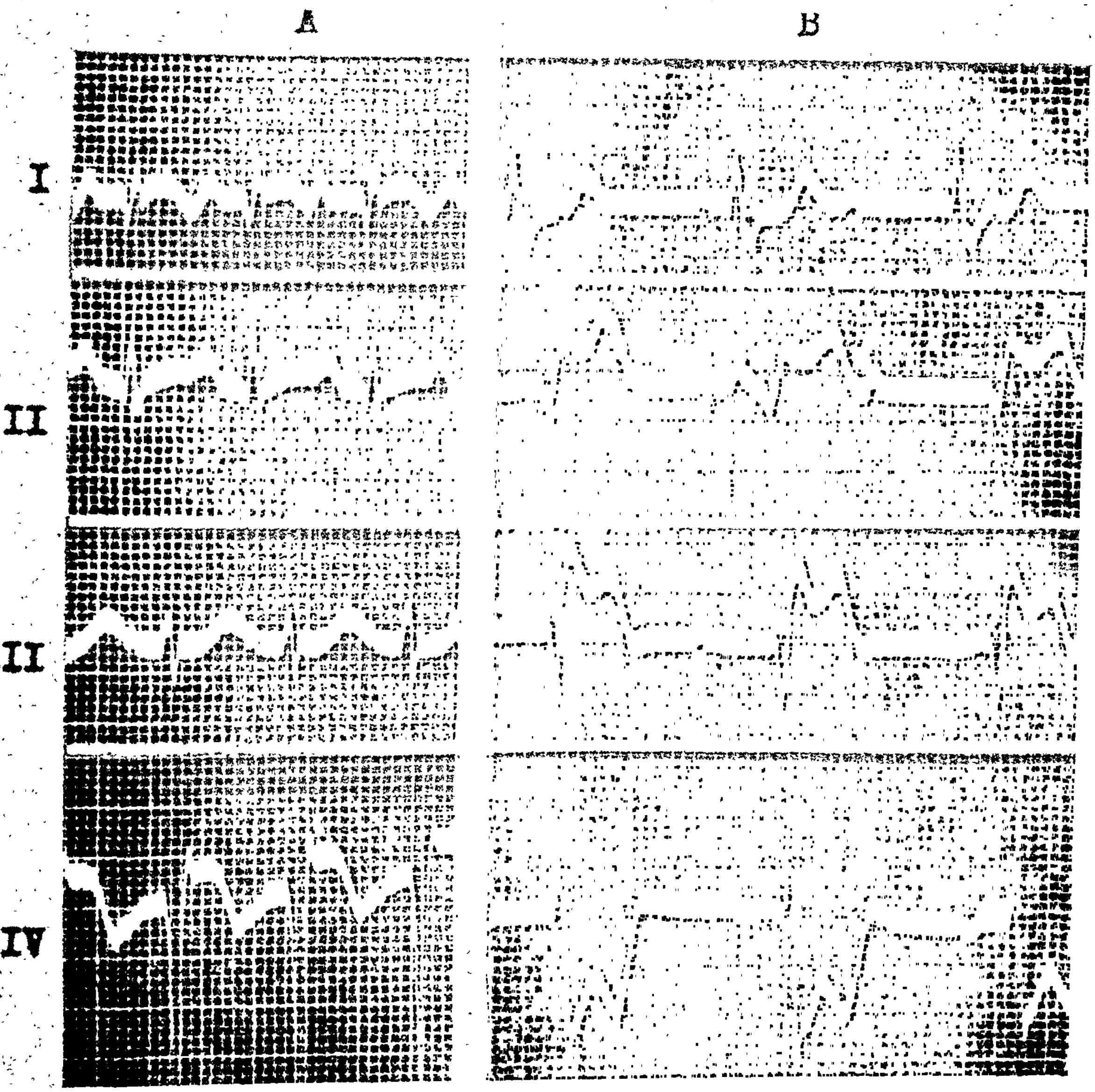

Fig. 1*A*.—Case 44. K. F., a man, 35 years of age. The electrocardiogram is characteristic of acute coronary occlusion with anterior wall infarction; it shows deep Q waves, elevation of the RS-T segments, and inversion of the T waves in Leads I and IV. There is a reciprocal relationship of the RS-T and T waves in Leads I and III. Autopsy—acute occlusion of anterior descending branch of left coronary artery, with infarction of anterior surface of left ventricle.

Fig. 1*B*.—Case 39. M. H., a man, 68 years of age. The electrocardiogram is characteristic of acute coronary occlusion with posterior wall infarction; it shows deep Q waves and elevation of the RS-T segments in Leads II and III, depression of RS-T in Leads I and IV, and inversion of T_4. There are also complete heart block and intraventricular block as a result of infarction of the posterior portion of the septum. Autopsy—acute occlusion of the right coronary artery with infarction of the posterior aspect of the left ventricle and interventricular septum.

clusion is independent of outside influences, such as effort and excitement, and actually is most common during rest or sleep.[19] It is the end result of the progressive atherosclerotic process in a coronary artery, and the exact time of occurrence is a fortuitous event. Coronary insufficiency, on the contrary, is due to a sudden inadequacy of coronary blood flow, produced by a number of factors. Thus, unusual effort and emotion increase the work of the heart; acute hemorrhage, shock, tachycardia, heart failure, surgical operations, and aortic valve disease diminish the amount of blood flow through the coronary arteries. If either increased cardiac work or diminished coronary blood flow develops in the presence of coronary artery disease, the myocardium may become ischemic and, if the precipitating factor persists, necrosis of the heart muscle may ensue. Occasionally no discernible cause of

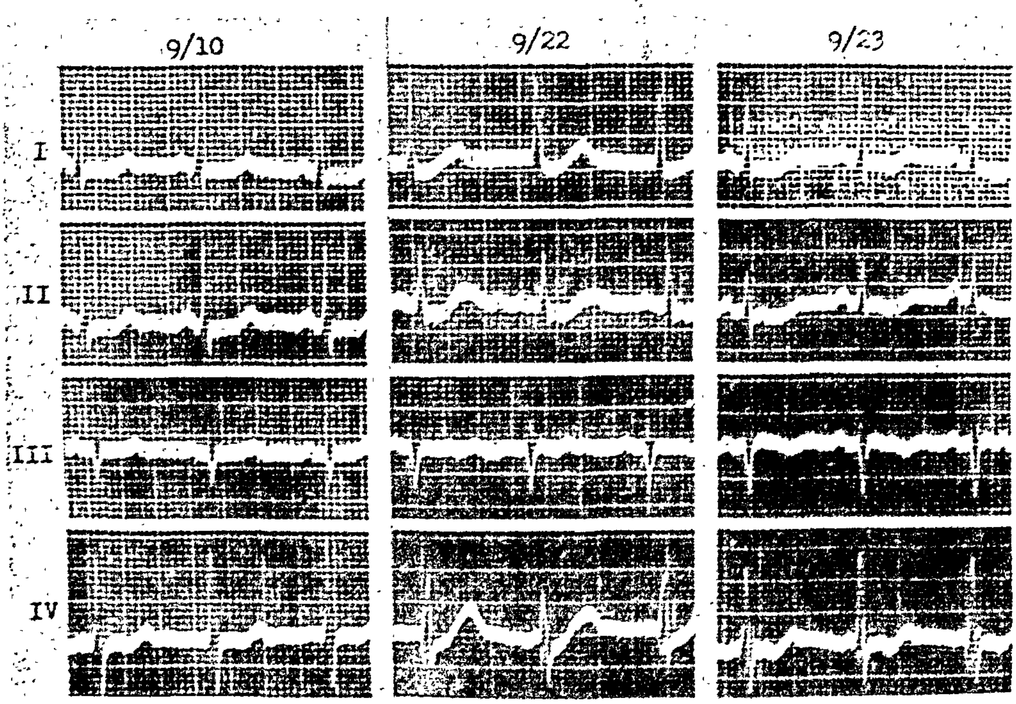

Fig. 2.—L. H., 494959, a woman, 55 years old, with hypertension and carcinoma of the stomach. Five days after subtotal gastrectomy she developed dyspnea, cyanosis, and signs of congestive and peripheral failure, and died five days afterwards. The preoperative electrocardiogram (9/10) showed left axis deviation and slight RS-T depression in Leads I and II. The electrocardiogram after the attack (9/22) showed increased depression of RS-T in these leads and depression in Lead IV. The next day (9/23) the T waves were diphasic in Leads I, II, and IV, and inverted in Lead III. The occurrence of RS-T depression and T-wave inversion, in the absence of RS-T elevation or deep Q waves, pointed to coronary insufficiency rather than to coronary occlusion. Post-mortem examination revealed a large embolus in the right pulmonary artery. There was no obstruction in the coronary arteries.

the coronary insufficiency is present. Unlike coronary occlusion, pain may be a minor symptom in coronary insufficiency, and sometimes is obscured entirely by the condition causing the ischemia, for example, shock or a surgical operation.[15] Even when present, the pain is often transitory. In other cases status anginosus may be present. In general, when no precipitating factor of an attack is apparent, the differential

diagnosis of coronary occlusion and insufficiency may depend on the electrocardiogram.

The electrocardiogram is considered characteristic of acute coronary occlusion when elevation of the RS-T segment and a deep Q wave are present in one or more leads (Fig. 1), with progressive change from RS-T elevation to T-wave inversion in serial records.

In acute coronary insufficiency the typical electrocardiographic changes consist of RS-T depression and T-wave inversion in two or more leads (Fig. 2). RS-T elevation and deep Q waves are absent. Unlike that in coronary occlusion, the electrocardiogram returns to its original configuration in several days or weeks.

MATERIAL

We have attempted to evaluate the clinical and electrocardiographic differences between coronary occlusion and coronary insufficiency by studying the 100 consecutive cases in which the diagnosis of coronary occlusion had been made or suspected by the physicians on the wards and which were examined post mortem. After death we reviewed the cases clinically and electrocardiographically and divided them as follows:

Cases 1 to 49, with electrocardiograms considered characteristic of coronary occlusion because of the presence of Q waves and RS-T elevation, progressing into T-wave inversion. Therefore, it was predicted that coronary occlusion would be found at autopsy in these cases.

Cases 50 to 55, with bundle branch block appearing for the first time. The sudden occurrence of bundle branch block, in association with a typical history in a person of middle age, suggested the diagnosis of coronary occlusion.

Cases 56 to 60, with electrocardiograms characteristic of coronary insufficiency, i.e., RS-T depressions and T-wave inversion, progressing or retrogressing under observation. Because of the absence of Q waves and RS-T elevation we predicted that myocardial necrosis due to coronary insufficiency, without occlusion, would be found at autopsy.

Cases 61 to 62, presenting the typical electrocardiographic pattern of pulmonary embolism, i.e., large S_1 and Q_3, and T_4 inverted.

Cases 63 to 100, a nondescript clinical group with nonspecific electrocardiographic changes. Because of the absence of any characteristic or progressive electrocardiographic pattern, such as those found in the preceding groups, neither coronary occlusion nor coronary insufficiency could be diagnosed clinically. This group included a very heterogenous series of cases. In many, careful consideration of the history and clinical observations, as well as of the electrocardiogram, disclosed the fact that the preliminary diagnosis of coronary occlusion should have been discarded early. Thus, a number of cases were not cardiac at all; these included bronchopneumonia, cerebral accident, nephritis, and peritonitis. Among the cardiac cases were acute and chronic cor pulmonale, heart failure, and coronary occlusion and insufficiency. In many of these cases the electrocardiograms could not be used for several reasons. For example, sometimes only one or two records were taken at long intervals. In other cases the administration of digitalis confused the interpretation. In a number of cases the electrocardiogram previous to the attack was markedly abnormal, with large Q waves, RS-T deviations, T-wave

TABLE 11

ELECTROCARDIOGRAPHIC AND AUTOPSY OBSERVATIONS IN 100 CONSECUTIVE CASES OF SUSPECTED CORONARY OCCLUSION

CASE	ADM. NO.	AGE	SEX	ELECTROCARDIOGRAM	AUTOPSY				REMARKS
					OCCLUSION	INFARCT	NECROSIS	PERI-CARDITIS	
A. Electrocardiogram Considered Characteristic of Coronary Occlusion									
1. J. R.	443599	60	M	$Q_{2,3}$, $RT_{2,3}$ elevated, $RT_{1,4}$ depressed	L.C.*	+	-	-	
2. A. S.	431656	60	M	Q_4, RT_4 elevated, auricular fibrillation	L.A.D.†	+	-	-	
3. E. M.	444867	61	F	$Q_{2,3}$, $RT_{2,3}$ elevated	L.C.	+	-	+	
4. S. W.	450219	59	M	Q_4, RT_2 elevated, $T_{1,2,3}$ inverted	R.C.‡	-	+	-	
5. I. S.	425318	45	M	$Q_{2,3}$, $RT_{2,3}$ elevated, $T_{2,3}$ inverted	R.C.	+	-	-	
6. M. O.	457838	74	M	$Q_{1,2,3}$, $RT_{1,2,4}$ elevated	L.C.	+	-	+	
7. E. H.	463375	55	F	$Q_{2,3}$, $RT_{2,3,4}$ elevated	R.C.	+	-	-	
8. I. L.	458033	57	M	Q_4, $RT_{1,2,3,4}$ elevated	L.A.D.	+	-	+	
9. L. C.	460046	44	M	$Q_{3,4}$, $RT_{1,2}$ depressed, $T_{1,2,3}$ inverted	L.A.D. R.C.	+	-	-	
10. S. L.	452172	74	M	Q_1, RT_1 elevated, 2_1 inverted	L.A.D.	+	-	-	
11. M. S.	465417	51	M	$Q_{2,3}$, $RT_{2,3}$ elevated, $T_{2,3}$ inverted	R.C.	+	+	+	
12. L. C.	454753	43	M	Q_4, RT_4 elevated T_4 inverted	L.A.D.	+	-	-	
13. H. D.	446681	43	M	$Q_{1,4}$, $RT_{1,4}$ elevated, $RT_{2,3}$ depressed	L.A.D.	+	-	-	
14. J. S.	443387	47	M	$Q_{2,3}$, $T_{2,3}$ inverted	L.A.D.	+	-	-	
15. H. K.	466751	60	M	Q_3, RT_3 elevated, $RT_{1,2,4}$ depressed	R.C.	+	-	+	
16. M. R.	438083	54	M	Q_4, $RT_{1,2,3,4}$ elevated	L.A.D.	+	-	+	
17. L. S.	438516	42	M	$Q_{2,3}$, $RT_{2,3}$ elevated, RT_1 depressed	L.A.D.	+	-	+	
18. Z. W.	462881	54	M	$Q_{2,3,4}$, RT_4 elevated	R.C.	-	+	+	
19. J. D.	449072	55	M	$Q_{1,4}$, $RT_{1,4}$ elevated, $RT_{2,3}$ depressed	L.A.D.	-	+	-	
20. E. P.	452870	82	F	Q_1, $RT_{1,4}$ elevated, $RT_{2,3}$ depressed	L.A.D.	+	-	-	
21. M. H.	429651	72	M	$Q_{2,3,4}$, $RT_{1,2,3,4}$ elevated	L.A.D.	+	+	+	
22. A. K.	430289	59	M	$Q_{2,3}$, $T_{2,3}$ inverted	R.C.	-	+	-	
23. J. M.	387038	65	M	$Q_{2,3}$, RT_3 elevated, $RT_{1,4}$ depressed	R.C.	+	-	-	
24. D. B.	398067	56	M	$Q_{1,4}$, $RT_{1,4}$ elevated, $T_{1,4}$ inverted	L.A.D.	+	-	-	
25. B. V.	448363	50	F	Q_4, $T_{1,4}$, inverted	L.A.D.	+	-	-	

*L.C.—Left circumflex coronary artery.
†L.A.D.—Left anterior descending coronary.
‡R.C.—Right coronary artery.

26. A. L.	446600	50	M	$Q_{1, 2, 4}$, $RT_{1, 4}$ elevated, $RT_{2, 3}$ depressed	L.A.D.	+	–	–	
27. H. B.	406061	62	M	$Q_{2, 3, 4}$, $T_{2, 3}$ inverted	R.C.	+	–	–	
28. O. L.	407587	63	M	$Q_{1, 2}$, $RT_{3, 4}$ elevated, $T_{1, 2, 4}$ inverted	L.A.D.	+	–	–	
29. J. S.	407390	53	M	$Q_{1, 4}$, $RT_{1, 4}$ elevated, RT_3 depressed	L.A.D.	+	–	+	
30. P. S.	398088	55	F	$Q_{1, 4}$, $RT_{1, 4}$ elevated, RT_3 depressed	L.A.D.	+	–	+	
31. J. W.	413699	63	M	Q_4, $RT_{1, 4}$ elevated, $T_{1, 4}$ inverted	L.A.D.	+	–	–	
32. J. K.	385381	56	M	Q_4, T_1 inverted	L.A.D.	+	–	–	
33. N. D.	392407	60	M	$Q_{2, 3}$, $RT_{2, 3}$ elevated, $RT_{1, 4}$ depressed	L.C. R.C.	+	–	+	
34. R. T.	397182	51	F	$RT_{1, 4}$ elevated, $T_{1, 4}$ inverted	L.A.D.	+	–	–	
35. J. L.	399108	67	F	$Q_{2, 3}$, $RT_{2, 3}$ elevated, $RT_{1, 4}$ depressed	R.C.	+	–	–	
36. H. H.	472077	65	M	$Q_{1, 2, 4}$, RT_1 elevated, T_1 inverted	L.C.	+	–	–	
37. M. R.	476291	55	M	$Q_{2, 3}$, $RT_{2, 4}$ elevated, RT_1 depressed, $T_{2, 3}$ inverted	R.C.	+	–	+	
38. C. S.	477281	75	M	Q_4, $RT_{1, 4}$ elevated, $RT_{2, 3}$ depressed	L.A.D.	+	–	+	
39. M. H.	477591	68	M	$Q_{2, 3}$, $RT_{2, 3}$ elevated, RT_1 depressed	R.C. L.C.	+	–	+	
40. W. F.	477687	56	F	$Q_{1, 4}$, $RT_{1, 4}$ elevated, $T_{1, 4}$ inverted	L.A.D.	+	–	+	
41. D. K.	486395	47	F	$Q_{2, 3}$, $RT_{2, 3}$ elevated, $RT_{1, 4}$ depressed, $T_{2, 3}$ inverted	R.C.	+	–	+	
42. M. F.	379066	57	M	$Q_{2, 3}$, RT_3 elevated, $RT_{1, 4}$ depressed, $T_{2, 3}$ inverted	L.C. R.C.	+	–	–	
43. S. B.	387028	52	M	Q_3, $RT_{1, 2, 4}$ depressed, $T_{1, 2, 3, 4}$ inverted	L.A.D. R.C.	+	–	–	
44. K. F.	436371	35	M	$Q_{1, 2, 4}$, $RT_{1, 4}$ elevated, $RT_{2, 3}$ depressed, $T_{1, 4}$ inverted	L.A.D.	+	–	–	
45. M. G.	384952	46	M	$Q_{1, 4}$, $RT_{1, 4}$ elevated; $T_{1, 4}$ inverted	L.A.D.	+	–	–	
46. S. G.	404600	67	M	$Q_{2, 3}$, $RT_{2, 3}$ elevated, RT_4 depressed, $T_{2, 3}$ inverted	L.C.	+	–	+	
47. L. D.	414717	62	M	$Q_{1, 2, 3, 4}$, $RT_{1, 2, 4}$ elevated	L.A.D.	+	–	–	
48. S. I.	428761	54	M	RT_4 elevated, $T_{1, 2, 4}$ inverted	–	–	+	–	Postoperative coronary insufficiency
49. J. K.	483543	59	M	Q_3, $RT_{2, 3}$ elevated, $RT_{1, 4}$ depressed, T_1 inverted	–	–	–	–	Postoperative shock

TABLE II—CONT'D

CASE	ADM. NO.	AGE	SEX	ELECTROCARDIOGRAM	AUTOPSY				REMARKS
					OCCLUSION	INFARCT	NECROSIS	PERICARDITIS	
				B. Electrocardiogram Not Characteristic of Coronary Occlusion					
a. *Bundle Branch Block*									
50. M. K.	453380	65	M	Left B.B.B. Ventricular tachycardia	L.A.D.	-	+	-	
51. D. F.	383531	75	M	Left B.B.B. Prolonged P-R	R.C.	+	-	-	
52. T. B.	395287	58	M	Left B.B.B.	L.A.D.	+	-	-	
53. W. F.	444679	51	M	Left B.B.B. Complete A-V block	L.A.D. L.C.	+	-	+	
54. D. D.	387259	52	F	Left B.B.B.	R.C.	+	-	-	
55. S. F.	381691	46	M	Right B.B.B.	L.A.D. R.C., L.D.	+	-	-	
b. *Characteristic of Coronary Insufficiency*									
56. A. H.	436060	60	F	$RT_{1,2}$ depressed, $T_{1,2}$ inverted	-	-	-	-	Coronary insufficiency
57. S. B.	413383	55	F	$T_{2,3,4}$ inverted	-	-	-	-	Coronary insufficiency
58. M. R.	457972	60	M	$T_{1,2,3,4}$ inverted	-	-	-	-	Coronary insufficiency
59. J. C.	434920	68	M	$T_{1,2,3,4}$ inverted	-	+	-	-	Coronary insufficiency Pneumonia
60. B. W.	442487	64	M	RT_1 depressed, T_1 inverted	-	+	-	-	Coronary insufficiency
c. *Characteristic of Pulmonary Embolism*									
61. R. P.	384075	84	F	Q_3, RT_3 elevated, S_1	-	-	+	-	Pulmonary embolism
62. R. S.	385365	70	F	Q_3, RT_3 elevated, S_1	-	-	-	-	Pulmonary embolism
d. *Nonspecific*									
63. S. H.	402869	50	M	T_1 inverted	L.A.D.	+	-	-	
64. J. L.	381256	62	M	$T_{1,2,3}$ inverted	L.C.	+	-	-	
65. P. B.	386384	67	M	$T_{1,2,3}$ inverted	R.C.	+	-	-	
66. A. L.	458297	69	M	$T_{1,2,3,4}$ inverted, $RT_{1,2,3,4}$ depressed	L.A.D.	+	-	-	
67. A. V.	415936	61	M	T_1 inverted	R.C.	+	-	-	
68. A. G.	404952	52	M	$T_{1,4}$ inverted	R.C.	-	-	-	
69. M. H.	453889	70	M	$Q_{2,3}$, $T_{1,2,3}$ inverted (present before attack)	R.C.	-	+	-	

70. C. B.	434487	68	M	$T_{1,2,3}$ inverted	L.A.D.	–	–	–	
71. A. K.	445549	74	M	Q_3, $RT_{1,2}$ depressed	L.A.D.	+	–	–	
72. B. B.	376989	73	F	$RT_{1,2,3}$ depressed, $T_{1,2,3}$ inverted	L.A.D. R.C.	+	–	–	
73. M. E.	390038	36	F	Q_3, $T_{2,3,4}$ inverted (present before attack)	R.C.	+	–	–	
74. E. A.	455567	48	F	Hypertensive pattern	R.C.	+	–	–	
75. E. B.	422603	65	M	Hypertensive pattern	–	–	+	–	Coronary insufficiency
76. M. W.	421978	71	M	Q_3, RT_3 elevated, $T_{1,2,3}$ inverted (prior to attack)	–	+	–	–	Coronary insufficiency
77. A. K.	438614	68	M	Right B.B.B	–	–	+	–	Coronary insufficiency
78. I. R.	432200	67	M	$T_{2,3,4}$ inverted	–	–	–	–	Acute cor pulmonale
79. J. S.	467157	57	M	$T_{2,3}$ inverted	–	–	–	–	Acute cor pulmonale
80. A. G.	447269	45	M	Hypertensive pattern	–	–	+	–	Pulmonary embolism
81. A. E.	459042	73	M	Hypertensive pattern	–	–	–	–	Pulmonary embolism
82. W. S.	392658	60	M	Hypertensive pattern	–	–	–	–	Pulmonary embolism
83. S. S.	447331	69	M	Hypertensive pattern	–	–	+	–	Pulmonary embolism
84. L. S.	445536	59	M	$T_{1,2,3,4}$ inverted	–	–	–	–	Chronic cor pulmonale, heart failure
85. B. F.	395731	52	F	$T_{1,2,3,4}$ inverted	–	–	+	–	Heart failure
86. S. P.	463069	62	M	Q_3, $T_{1,2}$ inverted (prior to attack)	–	–	–	–	Heart failure
87. R. S.	456510	51	M	$Q_{2,3,4}$, $T_{1,2,3,4}$ inverted prior to attack)	–	–	–	–	Bronchopneumonia Heart failure
88. S. B.	434527	74	M	$T_{1,2,3}$ inverted, Q_3 (prior to attack)	–	–	+	–	Heart failure
89. M. N.	474767	60	M	$RT_{1,2}$ depressed, $T_{1,2,3}$ inverted	–	–	–	–	Heart failure
90. E. B.	434121	77	M	Hypertensive pattern	–	–	–	–	Heart failure, pneumonia
91. J. B.	433469	62	M	B.B.B. (prior to attack)	–	–	–	–	Heart failure
92. L. S.	461830	70	M	B.B.B. (prior to attack)	–	–	–	–	Heart failure
93. J. A.	463891	45	M	B.B.B. (prior to attack)	–	–	–	–	Heart failure
94. M. R.	449478	85	M	B.B.B. (prior to attack)	–	–	–	–	Heart failure
95. N. P.	435696	47	M	$T_{2,3}$ inverted	–	–	–	–	Bronchopneumonia
96. A. H.	431847	71	M	Normal	–	–	–	–	Postoperative pneumonia
97. M. F.	447501	46	M	$T_{1,2,3}$ inverted	–	+	–	–	Pneumonia
98. M. K.	434044	48	M	$RT_{1,2}$ depressed, $T_{1,2,3,4}$ inverted	–	–	–	–	Chronic nephritis
99. C. H.	459753	68	F	$T_{2,3}$ inverted	–	–	–	+	Cerebral accident
100. L. L.	461925	66	M	T_1 low	–	–	–	–	Peritonitis

inversion, or bundle branch block. There were seven instances of "hypertensive" records, i.e., left axis deviation, high voltage QRS, and RS-T depression and T-wave inversion in Lead I. In view of the indiscriminate clinical diagnoses and electrocardiographic changes, which were stationary in this group of cases, it was considered best not to make any prediction concerning what would be found at autopsy. Actually, in the majority of cases coronary occlusion had not been considered seriously, even clinically.

After we had thus predicted what would be found post mortem, the coronary arteries were studied minutely by multiple cross sections at 2 to 3 mm. intervals.[4] Numerous microscopic sections of suspicious areas in the vessel, as well as in the myocardium, were also examined. The accuracy of this method and the number of coronary occlusions detected by it compare favorably with any other method described.

RESULTS

The electrocardiographic and post-mortem observations in each case are presented in Table II. The characteristic pattern of acute coronary occlusion, consisting of RS-T elevations and deep Q waves, was present in the electrocardiogram in Cases 1 to 49, inclusive, and, therefore, it was predicted that coronary occlusion would be found post mortem. This prediction proved to be true in forty-seven cases (Cases 1 to 47), i.e., 96 per cent of the cases. Not only did the electrocardiogram enable us to make the correct diagnosis of coronary artery occlusion in these forty-seven cases, but, in addition, it correctly indicated the site of infarction (anterior or posterior) in forty-five. When infarction involves the anterior surface of the left ventricle, the Q wave and RS-T elevation appear in Lead I and the chest leads; in posterior infarction, Leads II and III show these alterations. It is evident that, when the electrocardiogram presents RS-T elevation and Q waves, the diagnosis of coronary occlusion is practically certain. The two exceptions (Cases 48 and 49) proved to be instances of postoperative coronary insufficiency; necrosis of the myocardium was found only in Case 48; the other patient died within eighteen hours, possibly too soon for anatomic changes in the myocardium to have occurred. In the latter case (Case 49), a very profound state of shock suddenly developed several days after a cholecystectomy; there was no pain. In Case 48 an attack of precordial pain and shock followed prostatectomy; the bladder became severely infected and the patient's condition steadily declined. In both cases coronary sclerosis of moderate degree was found post mortem, but no evidence of recent or old occlusion. The presence of RS-T elevation in both these cases suggests that the myocardial ischemia was very severe. In summary, the *electrocardiogram indicated coronary occlusion in forty-nine cases*, and it was found post mortem in forty-seven.

Bundle branch block was present in six cases (Cases 50 to 55), with a typical history of coronary occlusion, and the latter was found post mortem in all. The sudden appearance of bundle branch block in association with an acute attack of pain or shock should make one suspect

acute coronary occlusion as the precipitating cause. On the other hand, it is frequently impossible to make a diagnosis of acute coronary occlusion in the presence of a bundle branch block pattern, for it may have existed prior to the attack and may not change as a result of it. The presence of RS-T elevation and Q waves may not be significant because they may be intrinsic in the bundle branch block pattern and bear no relation to the acute attack. However, the sudden onset of bundle branch block is suggestive of recent coronary occlusion.

In Cases 56 to 60 there was progressive RS-T depression or T-wave inversion, or both, i.e., changes typical of coronary insufficiency, and in all five cases this was confirmed at autopsy, which revealed coronary sclerosis without occlusion. Myocardial necrosis was present in three cases. The electrocardiographic changes occurred after operation.

In Cases 61 and 62 the electrocardiogram was typical of pulmonary embolism, and this was present in both at autopsy. Although the electrocardiographic pattern of pulmonary embolism may simulate coronary occlusion with posterior infarction, the proper diagnosis can usually be made if the diagnosis of pulmonary embolism is considered.

The remaining group (Cases 63 to 100), as we have seen, included a heterogeneous collection of noncardiac and cardiac cases and various clinical pictures, without any specific electrocardiographic pattern, which made it impossible to anticipate the post-mortem observations. We have already pointed out that in the majority of these cases the diagnosis of coronary occlusion should not have been entertained clinically. At autopsy the causes of death were various, including heart failure, nephritis, pneumonia, peritonitis, cor pulmonale, coronary insufficiency, and coronary occlusion.

COMMENT

Our results amply confirm the value of the term "coronary occlusion." Not only does it embrace a typical syndrome, well known to every physican, but it is associated with a characteristic, progressive, electrocardiographic pattern. The attack usually consists of severe, prolonged substernal pain, some degree of shock, a change in the heart sounds, e.g., gallop rhythm, a pericardial rub, a fall in blood pressure, and, frequently, heart failure. Fever, leucocytosis, and a rapid sedimentation time usually appear on the second or third days. The pain is not relieved by nitroglycerin. When RS-T elevation and deep Q waves are present in the electrocardiogram, it is almost certain that coronary occlusion exists; that is, it is present in 95 per cent of the cases. Such accuracy compares favorably with any diagnostic procedure in medicine. Yet, some authors have advocated discarding the term "coronary occlusion" merely because of the rare exceptions in which this clinical picture and electrocardiographic pattern are produced by infarction without occlusion. It should be emphasized that

coronary insufficiency itself, with or without infarction, also is associated in the majority of cases with a specific electrocardiographic pattern, namely, RS-T depression and abnormal T waves in two or more leads. Thus, with occasional exceptions, coronary occlusion and coronary insufficiency can be readily differentiated.

It is true, as we have found, that in some cases, coronary occlusion does not produce characteristic electrocardiographic changes, but that fact also does not militate against the use of the term; the same holds for some instances of coronary insufficiency. These cases are usually the ones in which the electrocardiogram was previously abnormal as a result of old coronary occlusion, bundle branch block, or marked enlargement of the heart, and the advent of another occlusion or of coronary insufficiency may not alter the electrocardiogram significantly, or may produce equivocal or nonspecific changes. In such cases the presence of a precipitating factor, such as effort, emotion, shock, operation, or hemorrhage, should make one suspect coronary insufficiency without occlusion. In the latter, the pain not infrequently is mild, a pericardial rub is absent, and heart failure usually is not severe. Fever, leucocytosis, and rapid sedimentation time are, as a rule, less marked than in coronary occlusion.

The term "acute coronary insufficiency," in the restricted sense described by us, has been employed and accepted for a number of years in the foreign literature, particularly in Germany.[7-11] The term then appeared in the American literature.[12-15] Its differentiation from coronary occlusion was clear. Therefore, the recent attempts to alter the meaning of the term to embrace all types of acute coronary disease, including coronary occlusion, seem to us confusing and without advantage. It would still be necessary to separate coronary insufficiency, in the narrower sense of myocardial infarction without occlusion, from coronary occlusion. We have shown that 95 per cent of cases can be divided into acute coronary occlusion and acute coronary insufficiency clinically and electrocardiographically, and it does not clarify the problem to discard both of these useful concepts because 5 per cent of the cases do not fall into either of the two groups. For similar reasons we object to another recent suggestion, namely, the use of the term "coronary failure" to designate all acute coronary seizures, whether due to occlusion or to insufficiency. This ambiguous term would merely add to the confusion, and is quite unnecessary.

The terms "coronary occlusion" and "coronary thrombosis" may be used interchangeably, but the former is preferred by us because it has been shown in recent years that the commonest mechanism of occlusion is intimal hemorrhage which may result in damage to the overlying endothelium and secondary thrombosis, or may even occlude the lumen without thrombosis.[3, 4]

The concept of angina pectoris has undergone considerable changes and discussion in recent years. It is now generally agreed that the attack represents a temporary insufficiency of the coronary flow, and it has been suggested, therefore, that the term "angina pectoris" be discarded, and one such as transitory coronary insufficiency be employed. Theoretically this is justified. However, the classical syndrome of angina pectoris, including the typical substernal pain and its radiation, its relation to effort, excitement, cold, and eating, and its relief by rest and nitroglycerin, is so characteristic and firmly established that it would seem advantageous to retain the term to connote one type of coronary insufficiency (Table I). It differs from the more severe forms of coronary insufficiency in that anatomic alterations do not occur in the cardiac muscle. Clinically, the attack of pain is usually of short duration. Shock is absent, the heart sounds and blood pressure are not significantly altered, and a pericardial rub and heart failure do not appear. Fever, leucocytosis, and an increase in the sedimentation rate are absent. Immediately after the attack the patient returns to his previous condition, that is, he may feel entirely well. The electrocardiogram is usually normal, but the changes characteristic of coronary insufficiency, that is, RS-T depression and T-wave abnormalities, may appear transiently during the attack. RS-T elevations and Q waves are not encountered.

CONCLUSION

The clinical, electrocardiographic, and post-mortem observations have been evaluated in one hundred consecutive cases in which the diagnosis of coronary occlusion had been entertained clinically.

Acute coronary disease should be divided into coronary occlusion and coronary insufficiency. Each of these is associated with a characteristic electrocardiographic pattern, and coronary occlusion usually presents a typical clinical picture.

Coronary occlusion is produced by obstruction of a coronary artery, and usually results in a confluent infarction extending from endocardium to pericardium. It is not related to external factors. The electrocardiogram typically presents deep Q waves and RS-T elevations, progressing into T-wave inversions which persist for a considerable period.

In forty-nine cases there was an electrocardiographic pattern which was regarded as characteristic of coronary occlusion, and the latter was found post mortem in forty-seven of these. In addition, the electrocardiogram correctly indicated whether the infarction was anterior or posterior.

Not every attack of coronary occlusion results in typical electrocardiographic alterations; this is true chiefly of multiple, fatal attacks.

The presence of a bundle branch block pattern in the electrocardiogram frequently makes the diagnosis of coronary occlusion uncertain.

Coronary insufficiency is usually precipitated by some factor which increases the work of the heart or reduces the coronary blood flow. The clinical picture is variable. The electrocardiogram shows RS-T depressions and T-wave inversions which last several hours or days. At autopsy, disseminated areas of necrosis are found in the subendocardial layer and papillary muscle.

The term "angina pectoris" is useful to indicate a transitory attack of chest pain which usually appears on effort, with transient or no acute electrocardiographic changes.

When the characteristic electrocardiographic pattern of coronary occlusion occurs, occlusion will be found at autopsy in 95 per cent of the cases.

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ELECTROCARDIOGRAPHIC CHANGES IN UREMIA ASSOCIATED WITH A HIGH CONCENTRATION OF SERUM POTASSIUM: REPORT OF THREE CASES

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IN A previous communication[1] we demonstrated that defects of intraventricular conduction developed in two cases of uremia in which the concentration of potassium in the serum was increased abnormally. Similar electrocardiographic changes had been noted by two groups of investigators in studies of experimental animals rendered toxemic by the injection of potassium salts or by the production of anuria.[2-4] In our experience and that of others, this electrocardiographic pattern in association with a marked increase of concentration of potassium in the serum has occurred rarely among uremic patients.[1, 5, 6] During the spring of 1943, for a period of six weeks, we observed a patient in different phases of uremia. Numerous electrocardiograms and estimations of the concentration of potassium in blood serum were made simultaneously on this patient. During the last few days of life the serum potassium increased rapidly and an intraventricular conduction defect developed. We therefore thought it desirable to publish in detail the clinical course, pathologic observations, studies of renal function and of the chemistry of the blood, and electrocardiographic changes in these three cases. Evidence will be presented that death was due to potassium intoxication.

REPORT OF CASES

CASE 1.—The patient, who was 18 years of age, was the son of a farmer. The family history was irrelevant to his present illness. The patient had contracted mumps and chicken pox in childhood. Tonsillectomy had been performed when he was 5 years of age. The present illness began March 3, 1936, five weeks before admission; it followed exposure to rain, when he became chilly and felt sick all over. Three days later, swelling of the face and ankles appeared and his physician found albumin in the urine. The patient was put to bed for two weeks, and during this period the edema subsided.

On admission, April 7, 1936, physical examination revealed the patient's height as 69 inches (175 cm.) and weight as 147½ pounds (67 kg.). There was edema of the eyelids, grade 1 (on the basis of 1 to 4, in which 1 designates the mildest and 4 the most severe edema), but no anemia; the tonsils had been removed previously. The cardio-

Received for publication March 6, 1944.

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TABLE I

DATA ON BLOOD AND RENAL FUNCTION OF PATIENT 1

DATE	WHOLE BLOOD			BLOOD SERUM							BLOOD PLASMA			RENAL FUNCTION AND ECG
						POTASSIUM								
	HGB., GM. IN 100 C.C.	UREA, MG. IN 100 C.C.	CREATININE, MG. IN 100 C.C.	PROTEIN, GM. IN 100 C.C.	ALBUMIN, GM. IN 100 C.C.	MG. IN 100 C.C.	MEQ. IN 1,000 C.C.	SODIUM, MG. IN 100 C.C.	SULFATE, MG. IN 100 C.C.	N.P.N., MG. IN 100 C.C.	CHLORIDE, MG. IN 100 C.C.	CO_2 COMBINING POWER, VOL. IN 100 C.C.	CHOLESTEROL, MG. IN 100 C.C.	
4/ 8/36	14.1	38							6.5					
4/10/36		26		4.2	1.7				5.6	29			340	Urea clearance 45 c.c. (maximum); sulfate clearance 12 c.c.
7/ 1/36	13.9	18		4.1	1.9				5.9	20				
10/ 3/39	4.3	220	13.2	4.9	1.9				21.0	157	615	28		ECG (2) A.M., P.M.
10/ 4/39														ECG
10/ 5/39		266	15.2			27.8	7.1						181	ECG
10/ 7/39														ECG
10/ 9/39		392	18.4			40.9	10.5	290						ECG*
10/10/39† 3:10 A.M.														

*Tracings taken and blood withdrawn for chemical studies nineteen hours before death.
†Patient died.

vascular system was objectively normal. However, the initial blood pressure was 150/80. The ocular fundi were normal. A roentgenogram of the chest was reported negative. Routine urinalyses, four in all, showed a specific gravity of 1.010 to 1.020, no reducing substances, and a large amount of albumin (grade 4); the sediment contained a moderate number of hyaline and granular casts, erythrocytes, and leucocytes. A high serum sulfate and a decrease in the clearance of both urea and sulfate indicated diminished renal function. During the patient's stay of six days in the hospital, the edema disappeared and his weight decreased 9¾ pounds (4.4 kg.). For studies of blood and renal function, see Table I. Our diagnosis was acute or subacute glomerulonephritis.

Two and a half months later a checkup revealed a healthy looking young man except for slight edema of the legs in the pretibial regions. The blood pressure was 130/85. Routine urinalysis still revealed a heavy precipitate of albumin, and, in the sediment, erythrocytes (grade 3).

The patient appeared to live comfortably for the next three years, working as a bookkeeper. Occasionally he noticed slight edema of the eyelids, but this would disappear after a night's rest. Two weeks before his return to the clinic a respiratory infection, accompanied by a dry cough and dyspnea, developed.

On the patient's third admission, Oct. 2, 1939, he appeared anemic and orthopneic; there was edema, grade 1, of the face and back and grade 2 of the legs. He weighed 155½ pounds (70.5 kg.). The heart was enlarged, measuring, on percussion, 3 | 12.5 cm. The heart rate was 106 per minute. There was an audible to-and-fro, leathery friction rub over the apex and base of the heart. There were moist râles over the bases of both lungs posteriorly and signs of consolidation in the right lower lobe. The blood pressure was 170/120. Examination of the ocular fundi showed edema of the disks of 3 and 2 diopters, scattered hemorrhages, and distinct narrowing of the retinal arterioles, i.e., signs of acute angiospastic retinitis. A roentgenogram of the thorax revealed evidence of bronchopneumonia in the lower part of the right lung. Routine urinalyses, six in all, revealed essentially the same results as on the previous visits, namely, a large amount of albumin, no reducing substances, and a sediment containing moderate numbers of hyaline and granular casts, erythrocytes, and leucocytes. There was a severe secondary anemia, with a concentration of hemoglobin of 4.3 Gm. per 100 c.c. of blood. The flocculation reaction for syphilis was negative; the concentration of urea and creatinine was very high, namely, 220 mg. and 13.2 mg. in 100 c.c. of blood, respectively, and there was a moderate reduction of the carbon dioxide combining power of the plasma (Table I). Thus, it was clear that the patient was suffering from chronic glomerulonephritis, severe renal insufficiency, uremia, anemia, hypertension, myocardial degeneration and failure, bronchopneumonia, and pericarditis.

Course in Hospital, Oct. 2 to 10, 1939.—The patient's temperature rose at times to 101° F. The volume of urine in twenty-four hours gradually decreased from 1,150 c.c. to between 100 and 300 c.c. during October 6, 7, and 8. A blood culture taken on October 3 failed to show any growth of organisms in forty-eight hours. On October 4 the patient was given a transfusion of 500 c.c. of blood, after which transitory pulmonary edema developed. The pericardial friction rub persisted

from the time of admission until death, on Oct. 10, 1939. Orthopnea, pain in the thorax, and apprehension were the patient's most troublesome symptoms. Electrocardiograms were taken on six occasions from October 3 to 9. The concentration of potassium in the serum was abnormally high, namely, 7.1 milliequivalents in 1,000 c.c. on October 5, but increased on October 9 to 10.5 milliequivalents in 1,000 c.c. (Table I). On this latter date the electrocardiograms showed great similarity to those of dogs poisoned by potassium (Fig. 1). On the following day, October 10, the patient died.

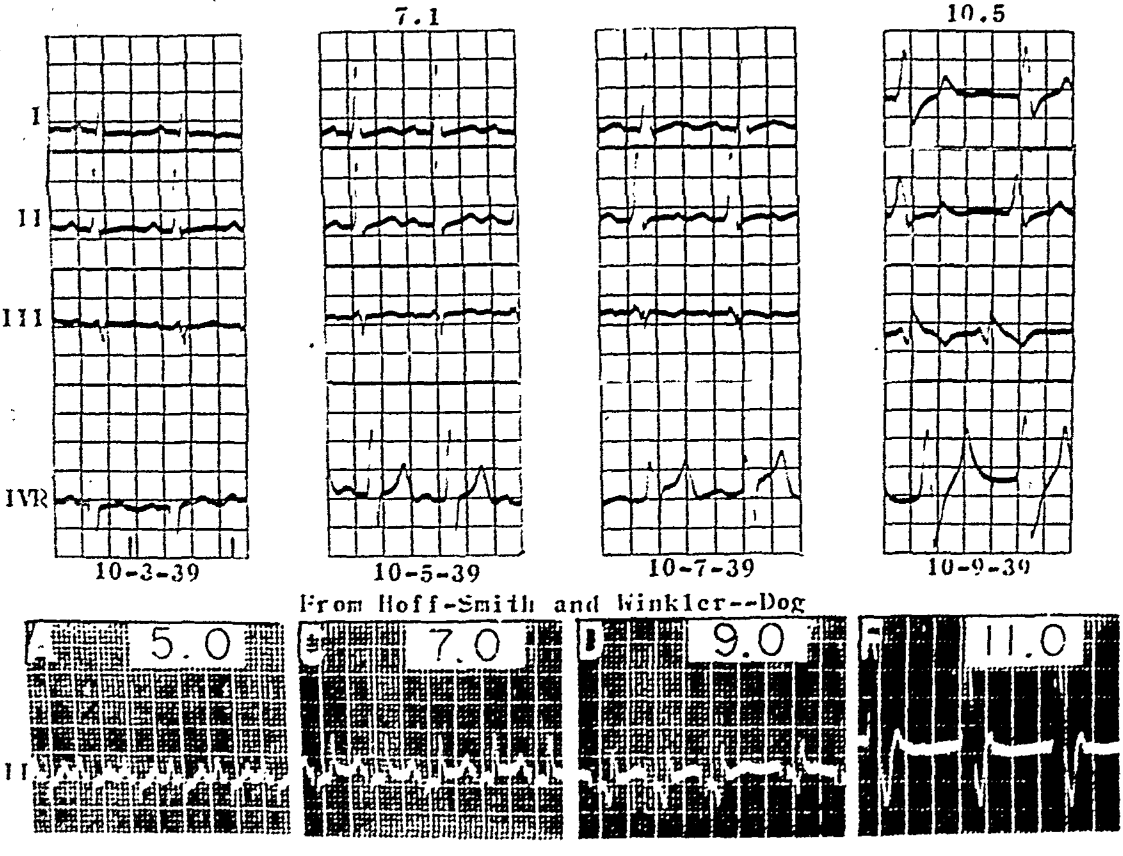

Fig. 1.—Electrocardiograms of Patient 1, which show progressive changes suggestive of po assium poisoning. In the first tracings (10/3/39) there is left axis deviation, with a shallow, diphasic T wave in Lead I. The second tracings (10/5/39) show an increase in the height of the T waves in all leads and a "peaked" appearance of the T wave in the chest lead. In the third tracings (10/7/39), delay of auriculoventricular conduction (P-R = 0.24 to 0.26 second) and widening of the QRS complex have made their appearance. In the last tracings (10/9/39), P waves cannot be identified, and there is a marked intraventricular conduction defect (QRS = 0.18 second). A few premature beats of probably ventricular origin are also present. Note similarity to tracings published by Hoff, Smith, and Winkler in their report on experimental intoxication with potassium (p. 608). Above the second and fourth tracings on Patient 1 are given the potassium content of the serum in milliequivalents as also noted, below, in the four tracings of the dog.

Necropsy.—There was moderate edema of the legs, and approximately 1,000 c.c. of clear fluid were present in the peritoneal cavity.

The heart weighed 740 grams. The epicardium was covered by fibrinous exudate. The walls of the left ventricle were thickened, and the ventricle was moderately dilated (Fig. 2*a*). Coronary sclerosis was graded 1.

There was chronic caseous tuberculosis in the lower part of the upper lobe of the right lung, with involvement of the hilar nodes. The lower lobe of the right lung was the seat of patchy bronchopneumonia.

The spleen weighed 230 grams, and was moderately congested. The liver weighed 2,245 grams, and was the seat of passive congestion of moderate degree. The lower end of the esophagus was covered by a pseudomembranous exudate. In the lower part of the ileum there were two small ulcers of Peyer's patches.

The right kidney weighed 140 grams. The surface was finely granular and the consistency was moderately increased. The markings of the cut surface were indistinct. The cortex was 0.6 cm. in width, and the medulla, 1.5 cm. The left kidney weighed 147 grams and had the same appearance as the right.

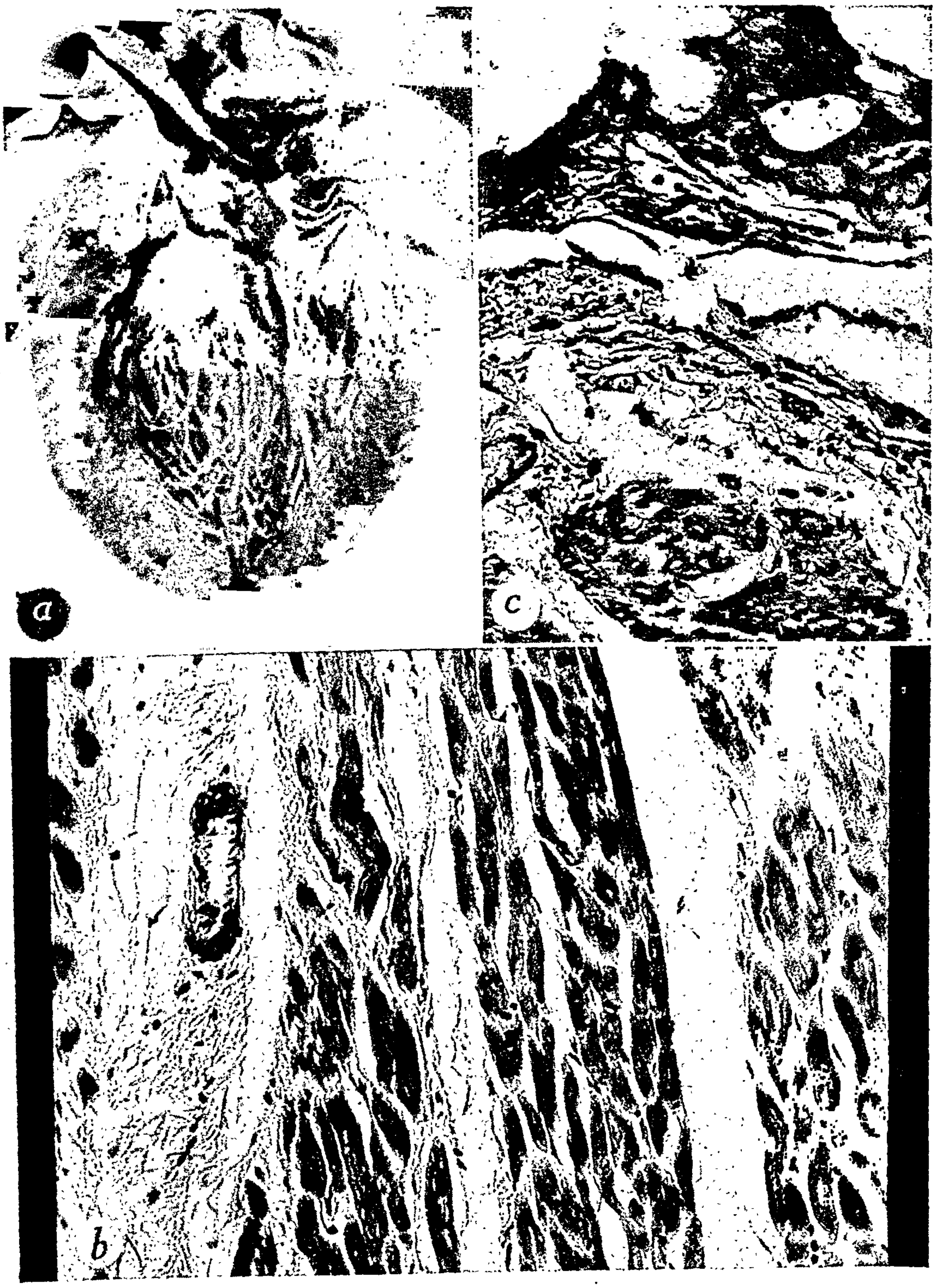

Fig. 2.—Patient 1. Heart. *a*, Severe hypertrophy and moderate dilatation of left ventricle. *b*, Normal myocardium (hematoxylin and eosin ×175). *c*, Fibrinous exudate on epicardium of left auricle (hematoxylin and eosin ×150).

Histologic Examination.—Sections of the myocardium appeared normal (Fig. 2*b*). Sections of the epicardium revealed a fibrinous exudate containing very few cellular elements. There was beginning organization of this exudate by fibroblasts from the epicardial surface.

Fig. 3.—Patient 1. Kidney. *a*, Hyalinization of glomeruli; dilatation of some tubules and atrophy of others; casts and erythrocytes in tubules; increase of interstitial connective tissue and lymphocytes (hematoxylin and eosin ×50). *b*, Same (hematoxylin and eosin ×150).

The appearance was consistent with that of so-called uremic pericarditis (Fig. 2*c*).

Sections of the right lung revealed progressive, nodular, caseous tuberculosis in the upper lobe. Sections from the lower lobe of the same

lung revealed tuberculous bronchopneumonia with much caseation. Between the regions of caseation, the alveoli were filled by large, clear, vacuolated phagocytic cells and lymphocytes. The ulcers in the ileum proved to be tuberculous in histologic sections.

Sections of both adrenal glands appeared normal.

Examination of many sections of both kidneys failed to reveal a single normal glomerulus. Most of the glomeruli were increased in size, and the capillaries were largely obliterated by an acidophilic, homogeneous, hyaline material (Fig. 3, *a* and *b*). The endothelial cells were encased by the homogeneous material and usually were diminished in numbers. Occasionally, glomeruli were observed in which some of the capillaries were still patent. Synechiae and epithelial crescents were numerous. The tubules were generally collapsed and lined by atrophied epithelium. A few of them were dilated, and most of them contained precipitated albuminous material. Lymphocytes and interstitial connective tissue were increased in amount. The arteries and arterioles revealed sclerosis graded 2.

The following anatomic diagnoses were made: (1) chronic glomerulonephritis, (2) fibrinous pericarditis, (3) hypertrophy of heart (hypertension), (4) chronic tuberculosis of the lungs, with tuberculous pneumonia and chronic tuberculosis of hilar nodes, (5) tuberculous ulcer of ileum, and (6) pseudomembranous esophagitis.

The duration of the renal disease in this case was three years and seven months.

Case 2.—The patient, aged 61 years, was an accountant. There were no facts in the family history pertinent to his present illness. As a child he had suffered from asthma. He had had pneumonia at the age of 23 years, pleurisy at 31, and influenza in 1918, when he was 39 years old. He also had had tonsillitis before 1920. Since May, 1939, or a year before the onset of the present illness, the patient had felt a heavy sensation under the lower part of the sternum, usually after the first swallow of solid food at the evening meal. This sensation was relieved by drinking water; however, four or five times a week he would vomit most of his supper within an hour after ingestion of the meal. The onset of cardiac symptoms occurred in May, 1940, seven months before admission, when dyspnea developed rather suddenly on exertion. Ten days later orthopnea became severe and edema developed. The patient was confined to bed for two months, and at the end of this period seemed to be greatly benefited by this rest. He was up and about from July 18 to October 1. On this latter date orthopnea and edema forced him to bed again. For the eight weeks preceding admission, coughing and nocturnal dyspnea had been the most irritating symptoms. The patient had noticed a diminishing volume of urine for some time. Treatment had consisted of digitalis and sedatives and three injections of merbaphen during November.

The patient was admitted to the hospital Nov. 27, 1940. He weighed 136 pounds (61.8 kg.), and his height was 65 inches (165 cm.). He was orthopneic, and considerable dependent edema was present, including the scrotum. The heart was enlarged, tachycardia was present, and some of the heartbeats did not produce a pulse in the radial artery. The heart sounds were distant. Gallop rhythm could be heard, but no murmurs. There were numerous moist râles throughout the lungs and signs of fluid in the right lower portion of the thorax. There was also

evidence of congestion of the liver; the edge was easily palpated 5 cm. below the costal margin. The blood pressure was 115/85. Dr. Wagener reported that the ocular fundi were essentially normal. Routine urinalyses, four in all, showed a specific gravity of 1.014 to 1.024, albumin, grade 1 to 2, no reducing substances, and a sediment containing hyaline casts, grade 3, and leucocytes, grade 1. There was no anemia; the erythrocytes numbered 4,480,000 per c.mm. The blood flocculation reaction for syphilis was negative. A roentgenogram of the thorax revealed an enlarged heart shadow (greatest diameter, 17 cm.) and some congestion at the bases of both lungs. The clinical picture was that of chronic myocardial degeneration and failure, with severe chronic passive congestion of the lungs, liver, and kidneys.

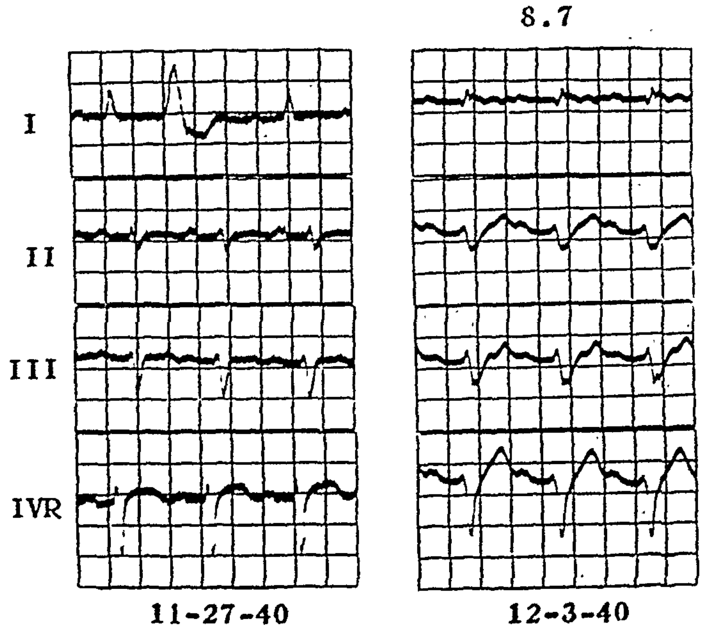

Fig. 4.—Electrocardiograms of Patient 2. The first tracings (11/27/40) show low amplitude, with slurring of the QRS complexes, isoelectric T waves in the standard leads, and left axis deviation. There are delayed auriculoventricular conduction (P-R = 0.24 second) and a few premature beats of ventricular origin. The second tracings (12/3/40) show that a marked intraventricular conduction defect (QRS = 0.16 second) has developed, with the P-R interval remaining the same; note potassium content of serum in milliequivalents.

Course in the Hospital from November 27 to December 7.—The blood pressure was measured each morning. It varied from 100 to 130, systolic, and 80 to 100, diastolic. The volume of urine voided in twenty-four hours was decidedly reduced, varying from 100 to 125 c.c. The clinical picture was characterized by vomiting, oliguria, increasing edema, and the rapid development of uremia. The blood urea increased from 48 mg. on November 27 to 246 mg. on December 6. On December 2 the patient began to be drowsy, and, on December 5, confused and stuporous, and from then until death, on December 7, there was increasing cardiac and renal failure. The administration of 12 Gm. of potassium nitrate in forty-eight hours during November 29 to December 1, of 2 c.c. of salyrgan on November 28, and of 2 c.c. of mercupurin on December 1 did not produce any diuresis, and therefore the use of these drugs was discontinued. Two electrocardiograms were taken, the first on November 27 and the second on December 3. The latter revealed a distinct intraventricular conduction defect (Fig. 4). On

December 3 there was also a high serum potassium concentration of 8.7 milliequivalents in 1,000 c.c. These findings were similar to those in Case 1. On December 6 a second estimation of the serum potassium revealed a concentration of 8.8 milliequivalents in 1,000 c.c. (Table II).

Necropsy.—There was severe edema of the legs and scrotum. The peritoneal cavity contained 200 c.c. of clear yellow fluid. There were 700 c.c. of clear, straw-colored fluid in the right pleural cavity, and 350 c.c. in the left pleural cavity.

Fig. 5.—Patient 2. Heart. Hypertrophy and severe dilatation of left ventricle with mural thrombi.

The heart weighed 485 grams. In the right auricle, at the orifice of the coronary sinus and immediately above the tricuspid valve, there was an old organized thrombus which measured 1.5 cm. in its widest extent. There were mural thrombi at the base of the right ventricle and also on the left lateral wall and apex of the left ventricle. The left ventricle was greatly dilated (Fig. 5). There was mild sclerosis of the coronary arteries.

There were mild congestion and edema of the lungs. Many of the small arteries of the lower lobes contained emboli and thrombi. There were recent, small infarcts in the regions supplied by these vessels.

The liver weighed 1,022 grams. The surface was smooth, but the markings were greatly increased on the cut surface. The so-called nutmeg appearance was present.

On the posterior wall and greater curvature of the stomach there were two superficial ulcers which had raised borders. The larger measured 4 by 1 cm., and the smaller, 2 by 1 cm. The jejunum and the

Table 11

Data on Blood of Patient 2

Date	Hospital Day	Whole Blood			Blood Serum					Blood Plasma		ECG
		Hgb., gm. in 100 c.c.	Urea, mg. in 100 c.c.	Creatinine, mg. in 100 c.c.	Protein, gm. in 100 c.c.	Albumin, gm. in 100 c.c.	Potassium, mg. in 100 c.c.	Potassium, meq. in 1,000 c.c.	Sulfate, mg. in 100 c.c.	Chloride, mg. in 100 c.c.	CO_2 combining power, vol. in 100 c.c.	
11/27/40	1	15.5	48									ECG
11/28/40	2				6.9	3.3						
11/29/40	3		74	2.2								
12/ 2/40	6		120	4.2					18			
12/ 3/40	7		142	4.8			34.2	8.7		500	46	ECG
12/ 4/40	8		162	5.1								
12/ 5/40	9		196	6.4								
12/ 6/40	10		246	6.8			34.4	8.8				
12/ 7/40* 11:22 P.M.	11											

*Patient died.

ileum were moderately congested. There were numerous small hemorrhages in the colon, measuring from 0.5 to 1.5 cm. in diameter. Some of these hemorrhagic regions were covered by a pseudomembranous exudate.

The right kidney weighed 182 grams. The surface was finely granular. There were one small cortical adenoma and two small scars which measured approximately 0.7 cm. in diameter. The left kidney weighed 165 grams and was not remarkable, grossly.

Fig. 6.—Patient 2. Scar of the interventricular septum of the heart (hematoxylin and eosin ×150).

Histologic examination.—In sections of the mural thrombus in the right auricle there were organization by fibroblasts and slight atrophy of the muscle fibers beneath the thrombus. In the thrombi of the right and left ventricles, also, organization had occurred, and there was also focal atrophy of the muscle fibers. Sections of the interventricular septum revealed moderate fatty metamorphosis in the muscle fibers and occasional foci of scarring (Fig. 6). In sections of the liver there was severe chronic passive congestion, with atrophy and necrosis of the cells in the central portions of the lobules.

Sections of the stomach revealed recent ulcerations of the mucosa. There were dilated capillaries and venules, together with small hemorrhages and thromboses in the base of the ulcers.

There were foci of atrophy, occasional collections of lymphocytes, and chronic passive congestion in sections of the adrenal glands.

In sections of the kidneys there was evidence of moderate, chronic, passive congestion. There were also foci of tubular atrophy, sometimes associated with hyalinized glomeruli (Fig. 7, *a* and *b*). Arteriolar sclerosis was mild. There was an old pyelonephritic scar in the right kidney.

The following anatomic diagnoses were made: (1) hypertrophy of heart (485 grams); (2) dilatation of left ventricle, with cardiac de-

compensation; (3) hydrothorax (right, 700 c.c., left, 350 c.c.), ascites (200 c.c.), and subcutaneous edema of legs; (4) mural thrombi of right auricle and both ventricles; (5) organizing infarct of right lung, with chronic pleuritis; (6) chronic passive congestion of stomach, with recent ulcers; (7) chronic passive congestion and atrophy of liver; (8) multiple hemorrhages of cecum; and (9) mild fatty metamorphosis of the myocardium.

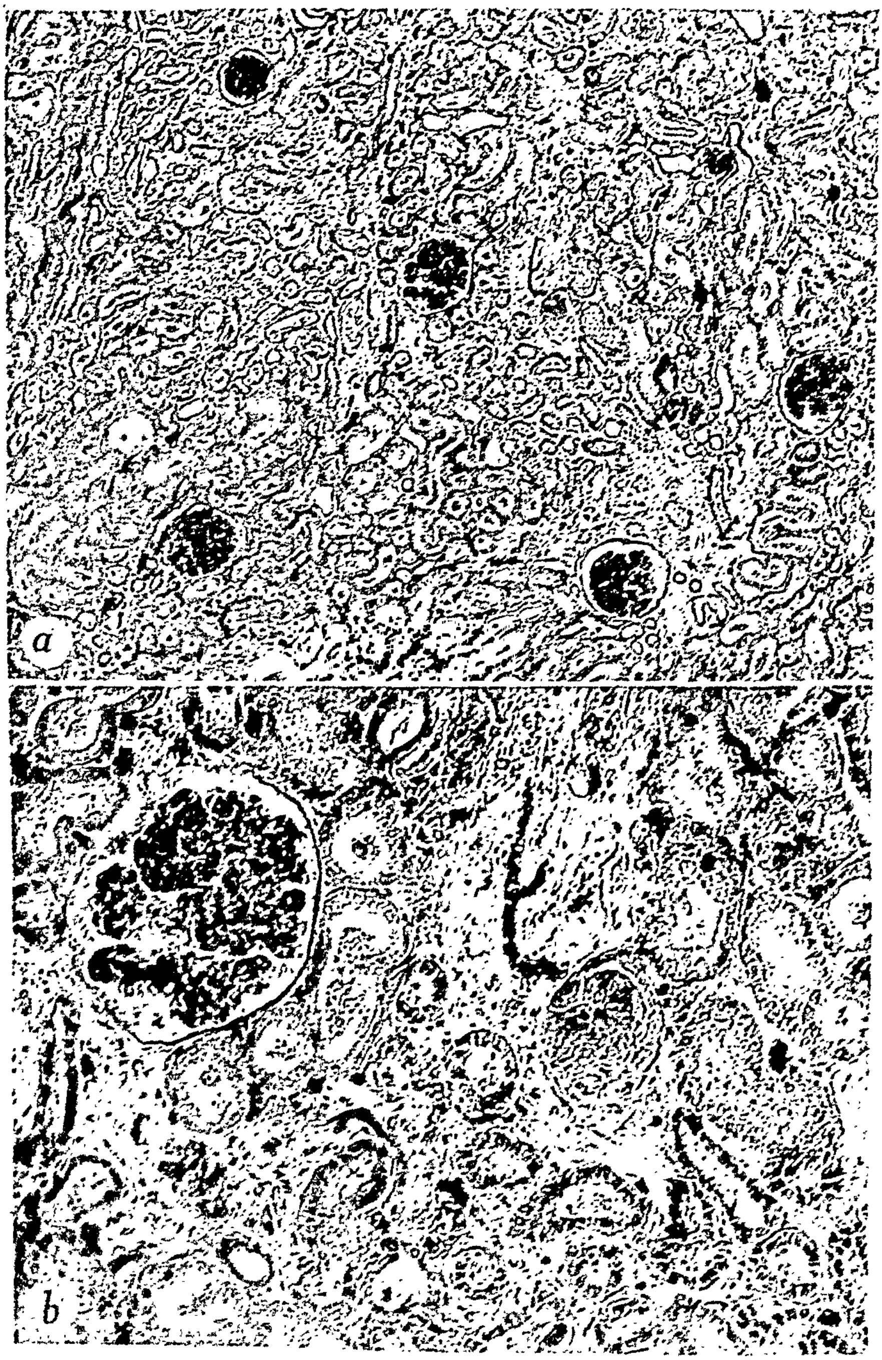

Fig. 7.—Patient 2. Kidney. *a*, Chronic passive congestion; foci of tubular atrophy (hematoxylin and eosin ×50). *b*, Same (hematoxylin and eosin ×150).

The duration of the chronic myocardial disease in this case was seven months, and that of the acute or subacute renal insufficiency, a few weeks.

CASE 3.—The patient was a married woman, aged 35 years, who first visited the Mayo Clinic Aug. 4, 1942. Her family history failed to reveal any facts of importance with regard to her present illness. The patient married at the age of 19 years, and had two healthy children, aged 14 and 12 years. There was no record of any serious illness in childhood or of untoward symptoms during her pregnancies. Her chief complaint was of irregular vaginal bleeding which had begun in February, 1942, six months before admission. On physical examination the patient appeared in good condition except for moderate anemia. She weighed 112½ pounds (51.0 kg.) and was 63 inches (160 cm.) in height. The heart seemed normal, and the blood pressure was 120/80. On vaginal examination one could see and feel an infiltrating type of carcinoma involving the cervix of the uterus. Further study revealed secondary anemia; the hemoglobin was 9.3 Gm. in 100 c.c., and the erythrocyte count, 3,500,000 per cubic millimeter. The blood flocculation reaction for syphilis was negative. The results of routine urinalysis were normal, as was the blood urea (24 mg. in 100 c.c.).

On August 17, Dr. Counseller performed abdominal hysterectomy according to the Wertheim technique, and, from the tissues removed, the pathologist made a diagnosis of carcinoma of the cervix and metastatic involvement of the tissues near the lower portion of the left ureter. The patient's postoperative course was very satisfactory. Subsequently, radium and roentgen therapy were used, and the patient left for home on September 16.

Interim History.—The patient felt well until the end of November. At that time nausea and vomiting, oliguria, and general edema developed. Actual anuria for six days occurred late in December. Ascites became marked at this time. Fluid was administered by vein, and soon the volume of urine increased and the edema and other symptoms subsided. The patient remained fairly well for the next two months. Her reasons for returning to the clinic were persistent thirst, polyuria, general weakness, and edema of the ankles.

Second Admission to the Mayo Clinic, March 17, 1943.—The patient weighed 101 pounds (45.9 kg.). She looked pale. There was no demonstrable edema. On bimanual palpation of the pelvis nothing abnormal was felt. The blood pressure was 120/80. A roentgenogram of the thorax was reported as not showing any abnormality except some calcified deposits in the lymph nodes of the hila of the lungs. The patient was observed in the hospital for a period of seventeen days—from March 19 to April 4. Routine urinalysis revealed a specific gravity of 1.003 to 1.011, no reducing substances, but albumin grade 1 to 2, and an occasional leucocyte in the sediment. The blood urea was increased to 172 mg., and the creatinine, to 6.0 mg. During the patient's stay in the hospital the blood urea fell to 140 mg. (Table III); the volume of urine in twenty-four hours increased from 1,600 to 3,000 c.c., and she felt distinctly better. Intravenous therapy included 5 and 10 per cent solutions of glucose and two transfusions of 250 c.c. of citrated whole blood. The patient was up and about in town for the next nine days. She re-entered the hospital on April 13 because of nausea and vomiting.

TABLE III

DATA ON BLOOD OF PATIENT 3

DATE	WHOLE BLOOD: HGB., GM. IN 100 C.C.	WHOLE BLOOD: UREA, MG. IN 100 C.C.	WHOLE BLOOD: CREATININE, MG. IN 100 C.C.	BLOOD SERUM: PROTEIN, GM. IN 100 C.C.	BLOOD SERUM: ALBUMIN, GM. IN 100 C.C.	BLOOD SERUM: POTASSIUM, MG. IN 100 C.C.	BLOOD SERUM: POTASSIUM, MEQ. IN 1,000 C.C.	BLOOD SERUM: SODIUM, MG. IN 100 C.C.	BLOOD SERUM: CALCIUM, MG. IN 100 C.C.	BLOOD SERUM: PHOSPHORUS, MG. IN 100 C.C.	BLOOD SERUM: SULFATE, MG. IN 100 C.C.	BLOOD PLASMA: CHLORIDE, MG. IN 100 C.C.	BLOOD PLASMA: CHOLESTEROL, MG. IN 100 C.C.	BLOOD PLASMA: pH	BLOOD PLASMA: CO_2 COMBINING POWER VOL. %	ECG
8/15/42	9.3	24														
3/18/43	6.3	172	6.0													
3/19/43												603			36	
3/23/43		100	4.4													
3/25/43	9.3															
3/27/43		130	5.6													
4/ 1/43		140	6.4									538			37	
4/13/43		218	10.8									602			35	
4/14/43		206									21				43	
4/19/43		200	13.6									462			40	
4/20/43		204	15.2			26.4	6.8					495				
4/21/43						27.4	7.0	293		8.8	23					ECG
4/23/43		201	16.8			26.8	6.9					528				ECG
4/26/43		183	15.2			24.6	6.3					544			42	ECG
4/30/43		132	11.2			20.4	5.2					507				ECG
5/ 7/43		160	8.8			26.3	6.7				15	596			39	ECG
5/10/43	8.0	177	9.6												45	
5/12/43		165				30.5	7.8				16	561			50	ECG
5/15/43		132	10.8			23.1	5.9									ECG
5/19/43	8.5	150	14.4	7.0*	4.4	23.9	6.1		9.7	6.6	15	540			50	ECG
5/22/43		165	16.8			26.2	6.7									ECG
5/31/43		246	18.0			32.1	8.2		9.7	4.8	27	468			31	ECG
6/ 3/43	7.8	267	22.0			36.6	9.4		9.1	10.1						ECG
6/ 4/43 10:00 A.M.														7.35†	32†	
10:55 A.M.						36.8	9.4	262	9.5							ECG‡
2:55 P.M.		291	21.0	6.1*	3.7					12.5	16	511	175§		25	
11:55 P.M. Pt. died																

*Nonprotein nitrogen of serum 120 and 192 mg. per cent, respectively.
†Oxalated blood withdrawn from arm vein under oil. CO_2 determined directly. pH determined (glass electrode) by Dr. Power.
‡Electrocardiogram taken and blood serum withdrawn for estimation of potassium concentration thirteen hours before death.
§Concentration of cholesterol esters 104, lecithin 169, fatty acids 366, and total lipoids 511 mg. per cent, respectively.

Course in Hospital April 13 to June 4, Fifty-Three Days.—On admission there was no demonstrable edema. The patient's weight was 100 pounds (45.4 kg.). Tachycardia was present, and gallop rhythm was heard over the cardiac apex. Her breath had a uremic odor and the blood urea had increased to 218 mg. Ophthalmoscopic examination revealed anemic fundi, with two small hemorrhages in the left retina which were considered to be secondary to the general anemia. The specific gravity of the urine varied from 1.002 to 1.010. The concentration of protein in the urine was accurately estimated in three twenty-four-hour collections of urine and found to be 0.09 to 0.8 per cent. A rare hyaline cast and a few to a moderate number of leucocytes were observed in the urinary sediment.

The volume of urine for the twenty-four-hour period, April 14 to 15, was 3,050 c.c. It gradually decreased to only 200 c.c. on April 18 and 19, but increased to 1,600 c.c. on April 23. On April 20 cystoscopic examination was done. The bladder and ureteral orifices appeared to be normal, but the ureteral catheter met definite resistance in both ureters at approximately 4 cm. from their vesical orifices. Passage of the catheters beyond the obstructions was not attempted. On April 21 the first of a series of twelve electrocardiograms was taken, and the concentration of serum potassium was found to be increased to 7.0 milliequivalents in 1,000 c.c.

TABLE IV

DISTRIBUTION OF ELECTROLYTES IN BLOOD PLASMA AND SERUM OF PATIENT 3*

BASE			ACID		
	MG. IN 100 C.C.	MEQ. IN 1,000 C.C.		MG. IN 100 C.C.	MEQ. IN 1,000 C.C.
Sodium	262.0	114.0	Chlorides	306.0	86.3
Potassium	36.8	9.4	Bicarbonate	32.0†	13.5
Calcium	9.5	4.7	Phosphates	12.5	7.3
			Sulfates	16.0	3.3
			Protein	6.1‡	14.8
Total meq.		128.1§			125.2

*Blood withdrawn 6/4/43 at 10:00 A.M., 10:55 A.M., and 2:55 P.M.

Estimations made in oxalated blood plasma—chlorides, bicarbonate.

Estimations made in blood serum—sodium, potassium, calcium, phosphates, sulfates, proteins.

†Blood withdrawn (oxalated) under oil, carbon dioxide content, volumes in 100 c.c. Plasma pH 7.35 estimated by glass electrode by Dr. Power.

‡Protein concentration estimated Gm. in 100 c.c. serum. Base meq. per liter bound by protein = 0.243 times Gm. protein per liter.[25]

§Magnesium was not estimated. Usual concentration among similar patients with uremia 2 to 3 meq.

With the rise in the volume of urine to 1,600 c.c. on April 23, diuresis began, and, on the following days, the volume rose to 1,775 and 2,750 c.c. This diuresis was accompanied by loss of weight, diminishing edema, improvement of the patient's well-being, and a fall of the concentration of urea, creatinine, and potassium in the blood; the potassium decreased to a normal concentration of 5.2 milliequivalents in 1,000 c.c. (Table III). The high fluid intake during this period included intravenous injections of solutions of 5, 10, and 20 per cent glucose, 5 per cent sodium bicarbonate, 0.9 per cent sodium chloride, and 50 per cent sorbitol. Theophylline with ethylenediamine was often added to these solutions in amounts of 0.25 to 0.5 Gm.

On May 1, thrombophlebitis developed in the left femoral vein. From May 15 to June 4, when the patient died, she grew progressively worse. There were a gradual increase of edema and a corresponding gain of

weight to 117 pounds (53.1 kg.). Nausea and vomiting became very troublesome. Renal insufficiency steadily increased as oliguria developed. On May 12, mild pulmonary edema occurred and gallop rhythm was present. On May 18 the blood pressure was 210/120. On May 18 and May 20 convulsive seizures developed. The blood pressure on May 20 was found to be 220/115. The concentration of potassium in the blood serum on May 31 had increased to 8.2 milliequivalents in 1,000 c.c., and continued to increase to 9.4 milliequivalents on June 3 and June 4 (Table III). On these two latter days the electrocardiograms revealed partial auriculoventricular block and intraventricular block (Fig. 8). Changes in the concentration of other electrolytes in the blood at this time are also of interest (Table IV). During the morning of June 4 the patient was drowsy and complained of a great deal of nausea. The blood urea and creatinine had risen to 291 and 21 mg. per 100 c.c., respectively. At 11:55 P.M. the patient died.

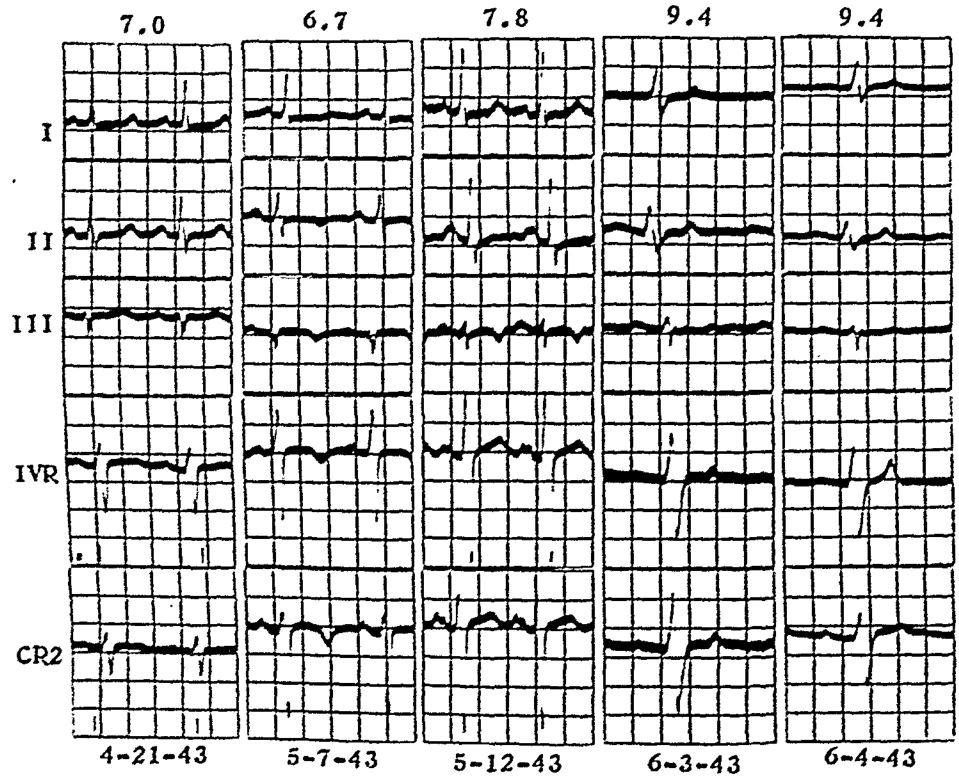

Fig. 8.—Electrocardiograms of Patient 3. The first tracings (4/21/43) show only left axis deviation and a slightly prolonged electric systole (QT = 0.32; QT/$\sqrt{\text{cycle}}$ = 0.41). The next tracings (5/7/43) show diphasic T waves in Lead I and negative T waves in all other leads. This picture, as described in the text, is sometimes associated with left ventricular hypertrophy. In the following tracings (5/12/43) the T waves in Lead I and chest leads have returned to an upright position. The next tracings shown (6/3/43) illustrate a lowering of the amplitude of the P waves, an increase of auriculoventricular conduction (P-R = 0.24 second), and the development of an intraventricular conduction defect (QRS = 0.16 second). The tracings taken the following day are very similar, and also to be noted is the sharp "peaked" T wave, with the narrow base in the apical chest lead. Note potassium content of serum in milliequivalents.

The clinical diagnosis in this case was bilateral, chronic hydronephrosis and pyelonephritis, secondary to bilateral ureteral obstruction due to metastatic carcinoma, renal insufficiency, uremia, hypertension, myocardial failure, and left ileofemoral thrombophlebitis.

Necropsy.—There was moderate subcutaneous edema which extended cephalad as far as the breasts. The left leg and thigh were noticeably

larger than the right. The peritoneal cavity contained approximately 1,500 c.c., and each of the pleural cavities contained approximately 1,000 c.c., of clear yellow fluid. In the left pleural cavity there were old fibrous adhesions situated laterally, anteriorly, and on the diaphragmatic surface. The transverse diameter of the pericardium was 15 cm., and the pericardial sac contained approximately 150 c.c. of clear yellow fluid.

The heart weighed 465 grams, as compared with an estimated normal of 250 grams, but was not otherwise remarkable. Coronary sclerosis was mild, grade 1.

There was a recent infarct 2 cm. in diameter in the upper lobe of the right lung. The lungs were not remarkable otherwise.

The gall bladder contained approximately 15 c.c. of dark brown bile. The mucous membrane appeared normal. There were four angular, shiny, black stones, approximately 3 mm. in diameter, in the cystic duct, and one in the gall bladder.

The stomach contained approximately 50 c.c. of clotted blood. There were moderate edema and congestion of the mucous membrane.

An irregular, firm mass, which measured 2.5 by 1.5 by 1 cm., surrounded and constricted the right ureter at a point 3 cm. cephalad to the ureteral orifice of the bladder. There was a similar mass 3 cm. in diameter around the left ureter at a point 2 cm. cephalad to the ureteral orifice. The ureters above the obstructing lesions and the pelves and calices of both kidneys were moderately dilated (Fig. 9). Aside from the hydronephrosis, the kidneys were not grossly remarkable. The right kidney weighed 174 grams, and the left kidney, 140 grams.

The upper portion of the left femoral vein was compressed by a small mass of firm white tissue. A firm gray thrombus occluded the left femoral and iliac veins in this region.

Histologic Examination.—Sections of the interventricular septum of the heart were normal for the most part. Rarely, small focal regions of atrophy and fibrosis could be observed (Fig. 10).

Sections from the region of increased consistency in the upper lobe of the right lung revealed an infarct which was undergoing organization at the edges. There were deposits of calcium in the alveolar septa and in the smaller vessels at the edge of the infarct. In sections of the liver there was moderate chronic passive congestion, with atrophy of the cells in the region of the central veins. There was mild chronic passive congestion in the adrenal glands.

In sections of the right ureter there were nests of squamous carcinoma cells throughout the wall, as well as in the connective tissue surrounding this structure. The neoplasm had grown into the submucosa and mucosa of the ureter, and, although a lumen was still present, it was definitely compromised (Fig. 11). The sections of the left ureter revealed a similar appearance.

In the sections of the right kidney there were moderate dilatation and atrophy of all tubules, together with an increase of interstitial connective tissue. Focal collections of lymphocytes and occasional accumulations of polymorphonuclear cells were observed (Fig. 12, *a* and *b*). There was dilatation of Bowman's capsule, but the glomerular tufts appeared normal. The left kidney was similar in appearance. There was mild arteriolosclerosis in both kidneys.

Sections of the left femoral vein revealed invasion of the wall by squamous-cell carcinoma. A partially organized and canalized thrombus occluded the lumen.

Fig. 9.—Patient 3. Obstruction of ureters by carcinoma with ureterectasis, hydronephrosis, and mild chronic pyelonephritis.

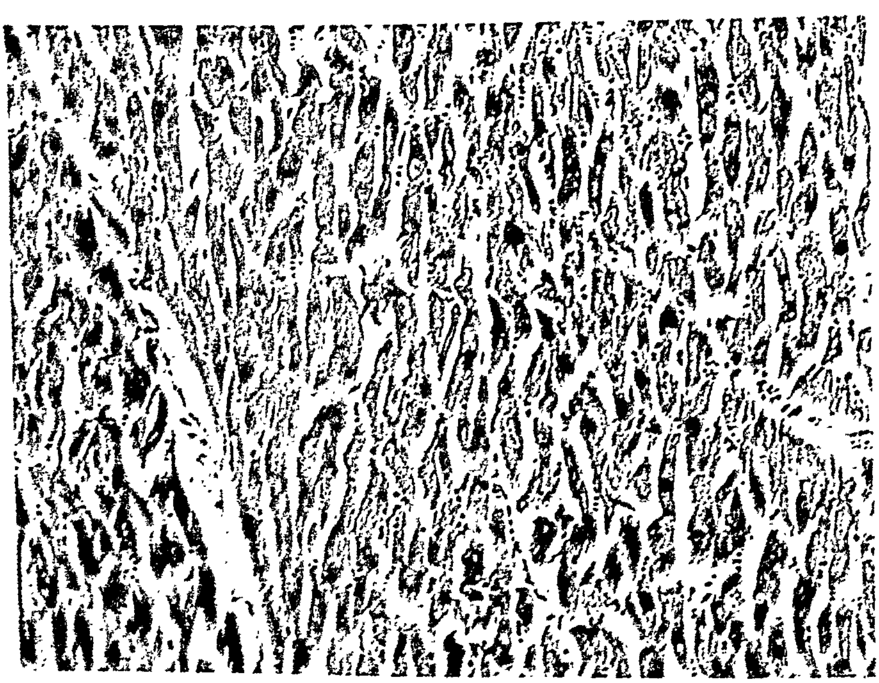

Fig. 10.—Patient 3. Interventricular septum; normal myocardium (hematoxylin and eosin ×150).

The following anatomic diagnoses were made: (1) ancient (Aug. 17, 1942) abdominal Wertheim hysterectomy for squamous-cell carcinoma of the cervix; (2) recurrent carcinoma, with obstruction of both ureters; (3) bilateral hydronephrosis and chronic pyelonephritis, with atrophy of kidneys; (4) metastatic carcinoma of left femoral vein, with organized thrombus; (5) organizing infarct of right lung; (6) bilateral hydrothorax (1,000 c.c. each), ascites (1,500 c.c.), and subcutaneous edema; (7) hypertrophy of heart (465 grams) (hypertension); and (8) gastric hemorrhage (50 c.c.).

Summary of Renal Insufficiency.—Symptoms of renal dysfunction began approximately ten months after cancer of the cervix was suspected and three and a half months after hysterectomy. Four periods of severe renal insufficiency developed between December, 1942, and June, 1943. Temporary improvement of renal function occurred after three of these periods. Death occurred when the patient had uremia, six months after the onset of symptoms due to renal insufficiency.

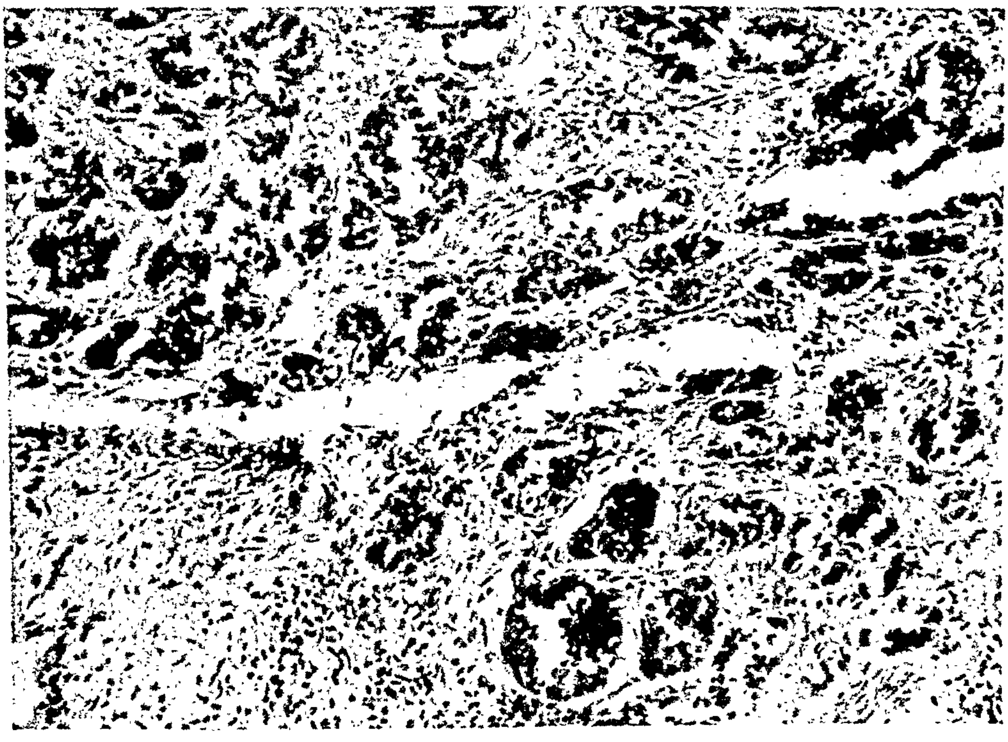

Fig. 11.—Patient 3. Squamous-cell carcinoma in wall of the right ureter (hematoxylin and eosin ×150).

OBSERVATIONS

Clinical and Pathologic Observations.—Severe uremia and oliguria were present in each of the cases when potassium intoxication was suspected. In Cases 1 and 3 the renal insufficiency and uremia were chronic, whereas, in Case 2, severe renal impairment and uremia were acute and present for only a week. Hypertension was noted in two of the cases, but was absent in Case 2 during the period of observation. The concentration of hemoglobin in the blood varied considerably in these cases—from normal to that of severe anemia. The cause and type of renal pathologic change were distinctly different in each case. The primary renal lesions were chronic glomerulonephritis in Case 1, chronic hydronephrosis and pyelonephritis secondary to ureteral obstruction

in Case 3, and chronic passive congestion secondary to myocardial failure in Case 2.

Our experience in Case 2 seemed unusual. However, Scholtz,[7] in 1932, reported an increased concentration of potassium in the serum of three patients, and commented on the absence of a renal pathologic process other than passive congestion. Bywaters[8] recently observed similar changes in the blood and electrocardiograms of patients suffering from acute renal insufficiency and uremia due to crush injuries of

Fig. 12.—Patient 3. Kidney. *a*, Atrophy of tubules, foci of leucocytes and increased interstitial connective tissue (hematoxylin and eosin ×110). *b*, Same (hematoxylin and eosin ×180).

the extremities. Therefore, it seems evident that the combination of uremia, increased serum potassium, and characteristically abnormal electrocardiograms occurs among patients suffering from both acute and chronic uremia. Hypertrophy of the heart and myocardial failure were present in all three cases before the marked increase of serum potassium and electrocardiographic alterations occurred. However, significant histopathologic lesions in the myocardium were found only in Case 2 (Fig. 6). The absence of distinct disease of the coronary arteries in these cases is worthy of comment. The presence of pericarditis in Case 1 and its absence in Cases 2 and 3 are also of interest.

Chemical Studies of the Blood.—Serious renal dysfunction was evident in the three cases at the period when the concentration of potassium in the blood serum was very high (8.7 to 10.5 milliequivalents in 1,000 c.c.), and changes had occurred in the electrocardiogram. These increased concentrations of potassium in the serum of our patients closely approximate the highest values reported in the serum of uremic patients.* The highest concentration noted in the literature was 11.6 milliequivalents.[9] Evidence of renal insufficiency was best indicated by marked retention of urea and creatinine in the blood stream; the concentration of urea increased to 246 to 392 mg. and that of creatinine to 6.8 to 22 mg. in 100 c.c. of blood. This degree of uremia presented an important, but complex, chemical problem. Special consideration was given to changes that occurred in the concentration of individual electrolytes and the acid-base equilibrium in plasma or serum. Associated with the marked and sustained increase in the concentration of potassium in the serum of these patients were an increase of sulfates and a slight to moderate decrease of the carbon dioxide combining power. The latter was indicative of acidosis, a common feature of uremia.

The concentrations of several lipoid constituents and a majority of the electrolytes were ascertained in Case 3 during the last day of the patient's illness, June 4. The concentration of the lipoid constituents was normal. The concentrations of potassium, sulfate, and phosphate were greatly increased; those of sodium, chloride and bicarbonate, were distinctly decreased. The concentrations of calcium and protein were normal. It is of interest that, with these definite quantitative alterations of both basic and acid components, the hydrogen ion concentration, or pH, of the plasma was within the normal range.[25] This nicety of balance between acid and basic radicles is also revealed by the relatively close approximation of the total milliequivalents of each. These values, 125 to 130 milliequivalents, are considerably lower than those observed among normal persons and in many cases of nephritis (Table IV). In 1928, Salvesen[10] reported similar low values for total base and total acid in a case of chronic glomerulonephritis during the terminal stage of uremia. In computing the total base in the serum of Patient 3, the

*We are referring to estimations of the concentration of potassium in the blood serum of uremic patients made since the introduction of a satisfactory micromethod.

amount of potassium relative to that of sodium is small. This indicates that the toxic action of the increased amount of potassium in the serum and tissue cells is not simply due to an increase of base per se.

The fluctuations of the concentration of potassium in the blood serum of Patient 3, during her stay of six weeks in the hospital, are interesting. The decrease from 6.8 milliequivalents on April 20 to 5.2 milliequivalents; a normal concentration, on April 30, was associated with improvement of renal function. Similar observations were made in a single case among a previous series of cases in which there was uremia.[1, 11] Later, in Case 3, the concentration of potassium increased to 7.8 milliequivalents (May 12). This increase was apparently temporary, for the concentration fell in three days to 5.9 milliequivalents. In contrast to these earlier fluctuations of the serum potassium there was a progressive rise from 6.7 to 9.4 milliequivalents during the terminal phase, from May 22 to June 4 (Fig. 13).

Electrocardiographic Observations.—It has been noted by us and others[6, 12-15] that increased serum levels of potassium are associated with rather characteristic electrocardiographic changes. Among normal persons, induced, mild hyperpotassemia causes increased height of the T waves, and the degree of increase of serum potassium correlates well with the increase in height of the T wave. Frequently this change becomes quite distinctive, in that the base of the T wave becomes narrower than normal and the apex sharp or "peaked." With greater and more sustained increases of serum potassium, as we have observed in our three cases of severe renal insufficiency, partial auriculoventricular block and intraventricular block may develop. The exact locus of the intraventricular block is unknown to us, and we feel that it would be wrong and misleading categorically to place it in the main bundle branches.

In regard to Case 1 it will be noted that pericarditis developed, and it is well known that this condition can alter the electrocardiogram greatly.[16, 17] In this connection it is of interest that we have observed in a case of uremia and pericarditis an electrocardiogram that was typical of pericarditis when the concentration of serum potassium was 4.6 to 5.3 milliequivalents. The only electrocardiographic change that might be related readily to pericarditis in Case 1 was the high, sharp T waves, with the elevated S-T segment, in the chest lead of Oct. 7, 1939. In the electrocardiogram of October 9 the tendency of the T wave to maintain its narrow base is to be noted, as well as the great similarity of the tracings to those of dogs poisoned by potassium (Fig. 1). The absence of the P waves with the maintenance of a regular rhythm could be associated with either auricular standstill or nodal rhythm with the P wave hidden in the QRS complex.

The records in the second case are not as extensive as in the others, but the sequence of defects of conduction which developed in the presence of a high serum potassium is obvious (Fig. 4).

The clinical and laboratory data are most extensive in the third case, and the records are complete over a period of six weeks. It is interesting that the electrocardiograms at first showed developing negativity of the T waves, and it is believed that this may indicate a change toward the patient's usual electrocardiographic pattern, rather than the reverse. During this period the serum potassium had decreased. The electrocardiograms next showed an increase of the voltage of the T waves (Fig. 8), and, concomitantly, the serum potassium increased. Later the electrocardiograms showed the same defects of conduction as in the other two cases.

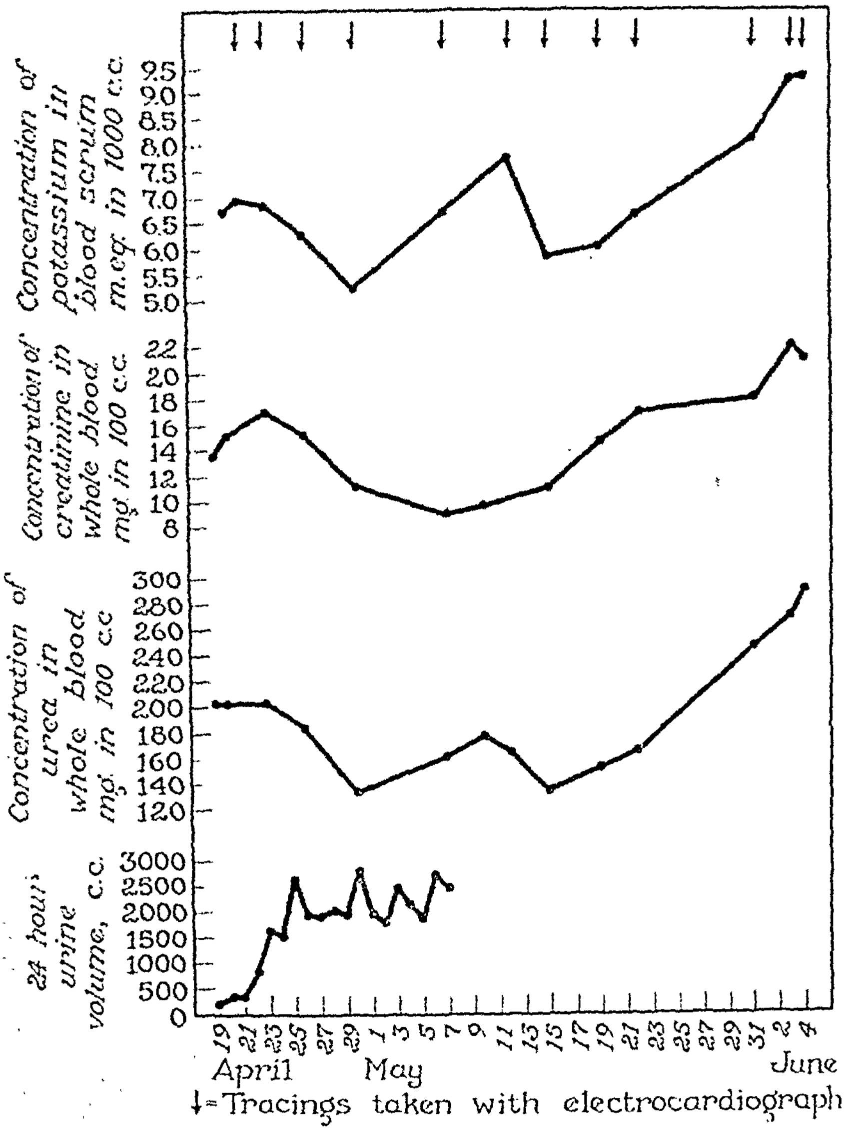

Fig. 13.—Patient 3. Fluctuations of certain constituents of the blood, volumes of urine collected in twenty-four hours, and dates when electrocardiograms were taken during observation in hospital from April 19 to June 4, 1943. Note decrease of blood urea, blood creatinine and serum potassium from April 23 to April 30, and concomitant rise of urinary volume; a steady progressive increase of urea, creatinine, and potassium in the blood from May 15 to June 4.

Premature beats, probably of ventricular origin, were observed in Cases 1 and 2, but not in Case 3. Digitalis was not given to Patient 1, a few small doses were given to Patient 2, and none was given to Patient 3 during the last sixteen days of her life. No potassium salts were administered to Patients 1 and 3.

The final estimation of the concentration of potassium in the blood serum of these patients varied between 8.8 and 10.5 milliequivalents. When, in Cases 1 and 3, the final electrocardiograms and estimations of serum potassium were made, nineteen and thirteen hours before death, respectively, intraventricular block was the striking feature. Finch and Marchand[18] observed similar changes in the electrocardiogram in a case of uremia when the concentration of potassium in the serum was 8.8 milliequivalents. Such changes occurred in the electrocardiograms of both dogs and cats which were given toxic doses of a salt of potassium, at a somewhat higher concentration of serum potassium. In the dog the range was 9.4 to 12, and, in the cat, 7.9 to 14.1 milliequivalents.

It has been demonstrated in both dogs and cats to which large doses of potassium salts have been given that, when intraventricular block has developed, recovery of the heart may occur.[2, 4] Such a recovery was observed by Sharpey-Schafer[19] in a case of aortic stenosis in which the patient ingested 15 to 20 Gm. of potassium salts. Ninety minutes later the concentration of potassium in the serum increased to 9.2 milliequivalents, and intraventricular block was evident in the electrocardiogram. We observed a similar course of events after giving 5 Gm. of potassium bicarbonate to a patient who had chronic nephritis and uremia.[20] The serum potassium of this patient increased in ninety minutes to 9.5 milliequivalents, and early intraventricular block was present in the electrocardiogram. Neither in this case nor in that of Sharpey-Schafer did any untoward symptoms develop, and the widening of the QRS interval subsequently disappeared. Therefore, in the experimental animal and among patients, intraventricular block associated with potassium intoxication is not necessarily an irreversible reaction. However, it should be emphasized that, when recovery from the intraventricular block occurred, the potassium toxemia was temporary, i.e., a matter of a few hours, whereas, in our cases, it was sustained for many hours. Bywaters[8] stated that he gave solutions containing insulin and glucose to a patient who had such an electrocardiogram and a high concentration of serum potassium with beneficial results. In his case severe renal insufficiency had developed after a crush injury to the extremities.

Ventricular fibrillation and death occurred in animals subjected to marked potassium toxemia.[2-4] These events occurred later in sequence than intraventricular block, and when the concentration of potassium in the blood serum was higher—14.7 to 15.8 milliequivalents in the dog and 14.2 to 28.1 milliequivalents in the cat. If death in our cases was due to potassium toxemia, one might suspect that a further rise of serum potassium and ventricular fibrillation occurred subsequent to our final observations. This period was nineteen hours in Case 1 and thirteen hours in Case 3. Finch and Marchand[18] in their Case 1 reported 10.5 milliequivalents of potassium in the serum when ventricular fibrillation and standstill occurred.

The duration of electric systole was disproportionately slightly prolonged in all three cases. In the first case, the Bazett,[21] the systolic index (QT/$\sqrt{\text{cycle}}$) varied between 0.40 and 0.44 until the last tracing, when it reached 0.52, which is high. In the second case the systolic index in the first tracing was 0.38, and, in the last tracing, it was 0.43. In the third case the systolic index at the beginning was 0.41. It stayed at about this value for three weeks, then decreased to 0.37 for two tracings, and finally returned to a figure of 0.42 in the tracings taken during the last two days. In this case, in which we have nine electrocardiograms with simultaneous determinations of serum potassium (Table V), there was no direct correlation between the systolic index and serum potassium level. With certain unexplained exceptions there was a good correlation between the height of the T wave (IVR) and the height of the serum potassium (Table V, Fig. 8), a correlation which has been mentioned previously.

TABLE V

ELECTROCARDIOGRAPHIC DATA AND SERUM POTASSIUM OF PATIENT 3

DATE	QT/$\sqrt{\text{CYCLE}}$	VARIATION IN VOLTAGE OF T WAVE IN LEAD IVR, MV.	SERUM POTASSIUM, MEQ.
4/21/43	0.41	+0.20	7.0
4/23/43	0.44	+0.28	6.9
4/30/43	0.43	-0.10	5.2
5/ 7/43	0.48	-0.20	6.7
5/12/43	0.45	+0.25	7.8
5/22/43	0.37	+0.15	6.7
5/31/43	0.38	+0.25	8.2
6/ 3/43	0.42	+0.10	9.4
6/ 4/43	0.42	+0.28	9.4

COMMENT

For the last hundred years toxicologists[22] have known that potassium salts, when injected rapidly into the vein of an experimental animal, induce cardiac standstill and death. Since 1938 the subject has been reinvestigated in both the dog and the cat. The results of numerous experiments reveal contemporaneous changes in the blood and electrocardiogram.[2, 4] These alterations are a steady, abnormal increase of the concentration of potassium in the blood serum, and a regular sequence of changes in the electrocardiograms until death from cardiac failure occurs. A similar sequence of events has been observed, also, in experimentally produced uremia.[3] Fortunately, cases of fatal poisoning of human beings after the ingestion or injection of potassium salts have been notably few. In a single instance the concentration of potassium in serum was ascertained and electrocardiographic studies were carried out.[18]

As mentioned in a previous section, Sharpey-Schafer and one of us (N. M. K.)[20] have observed among patients after the ingestion of potassium salts the temporary production of intraventricular block and hy-

perpotassemia. These observations indicate that this stage of intraventricular block, produced by potassium toxemia, can be reversible when the toxemia itself is temporary and reversible. In one case of severe uremia in which the patient did not receive potassium salts, we reported in an earlier paper[1] a sustained, great increase of serum potassium and intraventricular block. Bywaters[8] had a similar experience. Such events were noted also in Case 3 of this series thirty-six hours before death. We think that one may therefore surmise, especially if one remembers what occurs in experimental uremia and in the single case reported by Finch and Marchand,[16] that the period when intraventricular block was evident in our cases was a stage in the sequence before terminal ventricular fibrillation and cardiac death occurred. Further studies nearer the time of death should reveal decisive evidence on this point.

There are several possible reasons why in our three cases the concentration of potassium in the blood serum did not reach as high a level as reported in the dog and the cat: (1) the possibility that the blood specimen may not have been drawn near enough to the time of death; (2) definite previous dysfunction of the myocardium, indicating a possibly diminished tolerance of that organ to potassium; (3) the possibility that, among patients who have uremia, the concentration of potassium in the serum never increases to the same height as it does in animals: for example, a species difference; (4) presence of acidosis in the blood; this was never severe among our patients; (5) changes in the concentration of other electrolytes in the blood serum; for example, increases of sulfate and phosphate, decreases of chloride and sodium; (6) a low concentration of calcium in the serum, suggested by Winkler and his co-workers[23] and by Wood and Moe;[24] this possibility was excluded, at least in Case 3, for the serum calcium was within the normal range; and (7) an increase of toxic nitrogenous metabolites other than the known nitrogenous compounds, such as urea, creatinine, or uric acid.

We believe that there is much circumstantial evidence to support the thesis that the cardiac deaths in our cases were due to potassium toxemia. If subsequent observations confirm such a thesis, it seems clear that the excessive concentration of potassium leads to an abnormal functional disturbance rather than to visible pathologic alterations in the heart. Thus we should have a good example of a disturbance of electrolyte balance leading to a fatal upset of cellular metabolism.

SUMMARY

Serial observations were made in three cases in which severe renal insufficiency and uremia developed. The study included clinical, biochemical, electrocardiographic, and pathologic observations. Consistent observations were a marked increase of the concentration of potassium in the blood serum and the development of an intraventricular conduction defect shortly before death from cardiac failure. These results support the thesis that death in these cases was due to potassium intoxication.

METHODS OF CHEMICAL ANALYSIS EMPLOYED IN THE PRESENT STUDY

Whole Blood

Hemoglobin.—Sanford, A. H., Sheard, Charles, and Osterberg, A. E.: The Photelometer and Its Use in the Clinical Laboratory, Am. J. Clin. Path. 3: 405, 1933.

Urea.—Van Slyke, D. D., and Cullen, G. E.: A Permanent Preparation of Urease, and Its Use in the Determination of Urea, J. Biol. Chem. 19: 211, 1914.

Creatinine.—Folin, O.: Laboratory Manual of Biologic Chemistry, Ed. 3, New York, 1922, D. Appleton and Company, pp. 149, 245, and 247.

Plasma

Chloride.—Osterberg, A. E., and Schmidt, E. V.: Estimation of Plasma Chlorides, J. Lab. & Clin. Med. 13: 172, 1927.

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Cholesterol Esters.—Bloor, W. R., and Knudson, Arthur: The Separate Determination of Cholesterol and Cholesterol Esters in Small Amounts of Blood, J. Biol. Chem. 27: 107, 1916.

Lecithin.—Youngburg, G. E., and Youngburg, Mamie V.: Phosphorus Metabolism: I. A System of Blood Phosphorus Analysis, J. Lab. & Clin. Med. 16: 158, 1930. Modified by Maclay, E.: 1937.

Fatty Acids.—Bloor, W. R.: The Determination of Small Amounts of Lipid in Blood Plasma, J. Biol. Chem. 77: 53, 1928.

Serum

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Albumin and Globulin Fractions.—Howe, P. E.: The Determination of Proteins in Blood—a Micro Method, J. Biol. Chem. 49: 109, 1921.

Kingsley, G. R.: A Rapid Method for Separation of Serum Albumin and Globulin, J. Biol. Chem. 133: 731, 1940.

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This method in our hands has checked with gravimetric procedures. The precipitation by sodium cobaltinitrite was allowed to proceed for forty-five minutes at ice box temperature in order to obtain a good, granular precipitate. If this and other steps are rigorously adhered to, the method is satisfactory.

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CONTINUOUS INTRAVENOUS ADMINISTRATION OF HISTAMINE: EFFECT ON THE ELECTROCARDIOGRAM AND SERUM POTASSIUM

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The effect of histamine on the electrocardiogram has not been studied extensively in man. Because of the increasing clinical use of histamine, further investigation along these lines appears justified and necessary in order to ascertain any heretofore unobserved toxic or permanent effects on the heart.

Schenk[1] was probably the first to study the electrocardiographic changes produced by histamine. He noted frequent ventricular extrasystoles and marked arrhythmia after large doses of histamine given subcutaneously in man.

Massione and Picchio[2] studied electrocardiographically the effects of administering 1 mg. of histamine intramuscularly to nine human subjects. For this they employed the usual three standard leads. They noted an increase in cardiac rate, a decrease in both auricular and ventricular systoles, and an increase in conduction time. They pointed out that histamine should be given only to persons with healthy hearts, for in two cases of myocarditis a distinct increase in auriculoventricular block was seen.

In 1929, Weiss, Robb, and Blumgart[3] used histamine as an agent for measuring the velocity of blood flow, and noted temporary inversion of the T wave in Lead II for some twenty to sixty seconds in a number of their subjects. Later, Weiss, Robb, and Ellis[4] studied the effect of both a single injection and continuous intravenous administration of histamine on Lead II of the electrocardiograms of fifteen persons who had normal cardiovascular systems. Those who were given a single intravenous injection showed progressive depression of the T wave and simultaneous acceleration of the heart rate. With return of the normal cardiac rate, the T wave assumed its original shape. The authors interpreted these changes as produced by the action of histamine on the coronary vessels or on the cardiac musculature. They reported that doses as small as 0.004 mg. per minute may cause a depression of all the complexes of the normal electrocardiogram, but that the effect is most marked on the T wave. With an increase in the dose, the degree of depression was increased until the T wave became inverted. The inversion of the T wave disappeared as the rate returned to normal, "sug-

Abstract of a thesis submitted by Dr. Peters to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

Received for publication May 24, 1943.

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gesting that the increase of rate was the result of histamine on the coronary vessels.''

Since comparatively little is known concerning the effect of histamine on the electrocardiogram, for only one other group of investigators (Weiss, Robb, and Ellis[4]) have studied the effect of intravenous administration on the electrocardiogram, and they used only Lead II, it was considered worth while to observe further the effect of this substance on all three standard leads and two precordial leads. Also, since the amplitude of the T wave is known to be influenced by abnormal levels of potassium, as has been observed in Addison's disease and in familial periodic paralysis, this study includes the effect of histamine on the serum potassium.

PROCEDURE

Electrocardiograms were made on twenty-five persons before, in the course of, and after the intravenous injection of histamine. These persons were in the horizontal position and in a fasting state. Seven of the twenty-five persons were women and eighteen were men. The ages of the women ranged from 21 to 59 years, with an average age of 35 years. and the ages of the men ranged from 23 to 66 years, with an average age of 45 years. Although these patients cannot be considered entirely normal, none was known to have any significant cardiac symptoms or disease, and each had had a thorough physical examination before treatment with histamine. The diagnoses in these cases included Ménière's syndrome, multiple sclerosis, headaches, arteriovenous fistula, tinnitus, postural vertigo, torticollis, angioneurotic edema of the hands, psychoneurosis, and Parkinson's disease. In eight cases the three standard leads were employed; in seventeen, two additional leads, namely, Leads CR_2 and IVR, were used. Patients who were to receive histamine were allowed to rest for approximately fifteen minutes before the preliminary electrocardiograms were made.

One per cent solution of procaine hydrochloride was used subcutaneously over the site of venous puncture to allay pain and apprehension and to prevent, as much as possible, acceleration of the heart during venous puncture. Continuous intravenous injection of histamine was then started; the rate was slow at first, and then was increased gradually by various increments. In most cases the rate was doubled at each increment. A set of three or four electrocardiograms was made after each increment. The solution contained 2.75 mg. of histamine diphosphate in 250 c.c. of physiologic salt solution. The rates at which it was injected were increased from 0.0017 to 0.044 mg. of histamine base per minute. The 2.75 mg. of histamine diphosphate contains 1 mg. of histamine base. The rates of administration of histamine in this paper are given in terms of histamine base. Nearly all of the patients were given 250 c.c. of the solution containing histamine. Immediately after completion of the intravenous injection, a final set of electrocardiograms was made. Occasionally another set of tracings was taken fifteen minutes later. From six to nine sets of electrocardiograms, consisting of three or four leads each, were made in each case. About five to ten minutes intervened between tracings.

For control, in three of the twenty-five cases further studies were carried out. Electrocardiograms were made in the same manner, but physiologic salt solution, only, was injected instead of the solution con-

taining histamine. In addition to these studies, the concentration of serum potassium was ascertained by the method of Kramer and Tisdall[5] in seventeen cases before and after injection of histamine.

RESULTS

In twenty-four of the twenty-five cases (96 per cent), histamine produced a definite effect on the electrocardiogram. This effect was chiefly loss of amplitude of the T wave. In some cases this loss of amplitude proceeded either to the isoelectric level or to inversion of the T wave in all four leads. The effect was brief. In one case (4 per cent of the twenty-five cases), that of a man, the administration of histamine at high rates failed to produce any effect on the electrocardiogram.

Age.—In order to ascertain the influence of the age of the patient on the changes in the electrocardiogram, the cases were arbitrarily grouped according to the degree and duration of change in the electrocardiograms after the injection of histamine. Four groups were formed. In the first group no changes were found in the electrocardiogram. Only one case fell in this group. In the second group certain slight effects were found. Seven cases were included in this group. All the patients were men, and their average age was 46 years. In the third group moderate changes were noted in the T waves during the administration of histamine, and these changes were present in most instances for a short time after the injection of histamine was discontinued. There were eleven cases in the group. Five of the patients were women and six were men. Their average age was 40 years. In the fourth group the T waves underwent the most marked changes, and, in general, these changes continued longest after the injection of histamine was stopped. Of the six patients in this group, two were women and four were men. The average age of these six patients was 41 years; the youngest patient was 21 years, the oldest, 56 years. Age alone, therefore, did not appear to be a significant factor in the changes in the electrocardiograms after the use of histamine. In all of the cases in group 4, except one, the effect of the drug was prolonged.

Serum Potassium.—The average concentration of potassium before the injection of histamine was 18.8 mg. per 100 c.c. of serum, and after the injection the average concentration was still 18.8 mg. per 100 c.c. In five cases a slight increase followed the injection; in seven, a small average decrease, and, in five, no change followed the injection. The serum potassium seems therefore to have little if any influence on the electrocardiographic complexes and not to be responsible for the changes observed after the injection of histamine.

T Waves.—The predominant effect of histamine seemed to be on the T waves (Table I). The T wave in Lead III most frequently showed the effect of histamine first. The average rate of administration of histamine in milligrams per minute at which the effects were first observed in the various leads is shown in the final column in Table I.

TABLE I

EFFECT OF HISTAMINE ON THE T WAVE

	CASES				AVERAGE RATE OF ADMINISTRATION (MG PER MIN.)
	LOSS OF AMPLITUDE	DEPRESSION TO ISOELECTRIC LEVEL	INVERSION	EFFECT FIRST OBSERVED*	
Lead I	20	2	0	6	0.025
Lead II	20	3	4	11	0.023
Lead III	16†	3	9	14	0.014
Lead CR_2	15	2	1	7	0.024
Lead IVR	12	1	0	6	0.027

*The T waves in more than one lead sometimes show effects at the same time.

†Five subjects already had inverted T waves in this lead, and four had either isoelectric or diphasic T waves in preliminary electrocardiograms.

These figures indicate that the T wave was most easily influenced in Lead III, and least so in Leads IVR and I.

The effect of histamine disappeared immediately after the administration was stopped in nine cases, and, in five other cases, it disappeared in all leads except one. It continued for at least five minutes in five cases, and was back to normal in three cases in ten to fifteen minutes. In only these three cases were electrocardiograms made more than ten minutes after discontinuation of the histamine. These three cases, in which the effect was known to have been lost in ten to fifteen minutes, in addition to the nine cases in which the effect of the drug was lost immediately after injection was discontinued, indicate that the influence of histamine is neither prolonged nor permanent. In two cases, in spite of continued and increased doses of histamine, the T wave recovered its voltage even before the injection of histamine was discontinued (Fig. 1).

One of the greatest effects on the electrocardiogram was produced in the case which follows:

This patient began to show the effect on the T waves of all leads when histamine was injected at the rate of 0.014 mg. per minute. Control electrocardiograms (Fig. 2, *A*) showed left axis deviation and an isoelectric T wave in Lead III. When histamine was injected at a rate of 0.0035 mg. per minute (Fig. 2, *B*), the T waves in Leads I and II began to lose voltage. This effect became more pronounced when the rate of injection of histamine was increased to 0.028 mg. per minute (Fig. 2, *C*). The T wave became isoelectric in Lead I, and inverted in Leads II and III. The T wave in both chest leads also became lower in amplitude. When 0.042 mg. of histamine base was injected per minute (Fig. 2, *D*), the T waves in Lead I and in Leads IVR and CR_2 had regained their former amplitude. In Lead III the T waves remained slightly inverted, but a striking observation in this case, too, was that, instead of a continuous depression of the T wave with increased amounts of histamine, an escape occurred, which was apparently due to some readjustment on the part of the heart, and was manifested by an increase in the amplitude of the T wave. The cardiac rate, however, had not returned to normal. Immediately after discontinuation of the histamine (Fig. 2, *E*), the T waves in Leads I, II, CR_2, and IVR

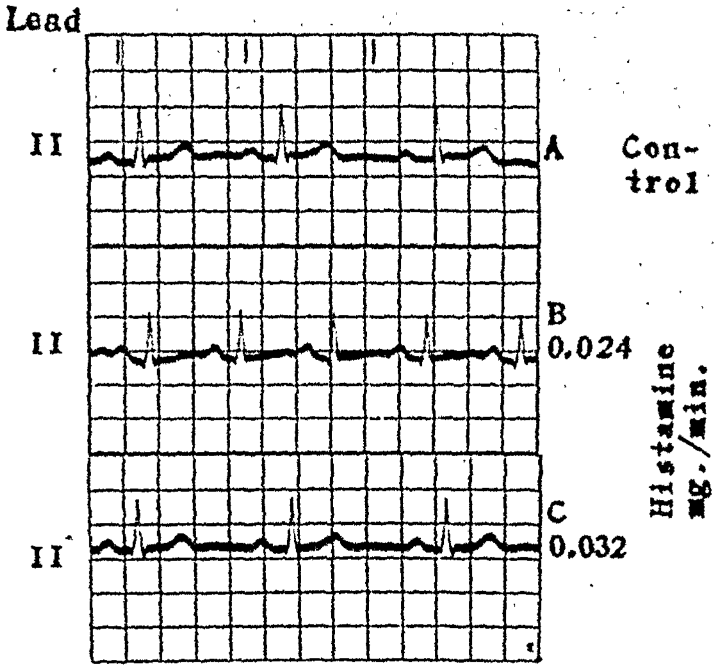

Fig. 1.—Electrocardiograms. *A*, Control; *B*, isoelectric T wave nine minutes after *A*; *C*, increase in T-wave amplitude ten minutes after *A*, in spite of continued and increased rate of administration of histamine.

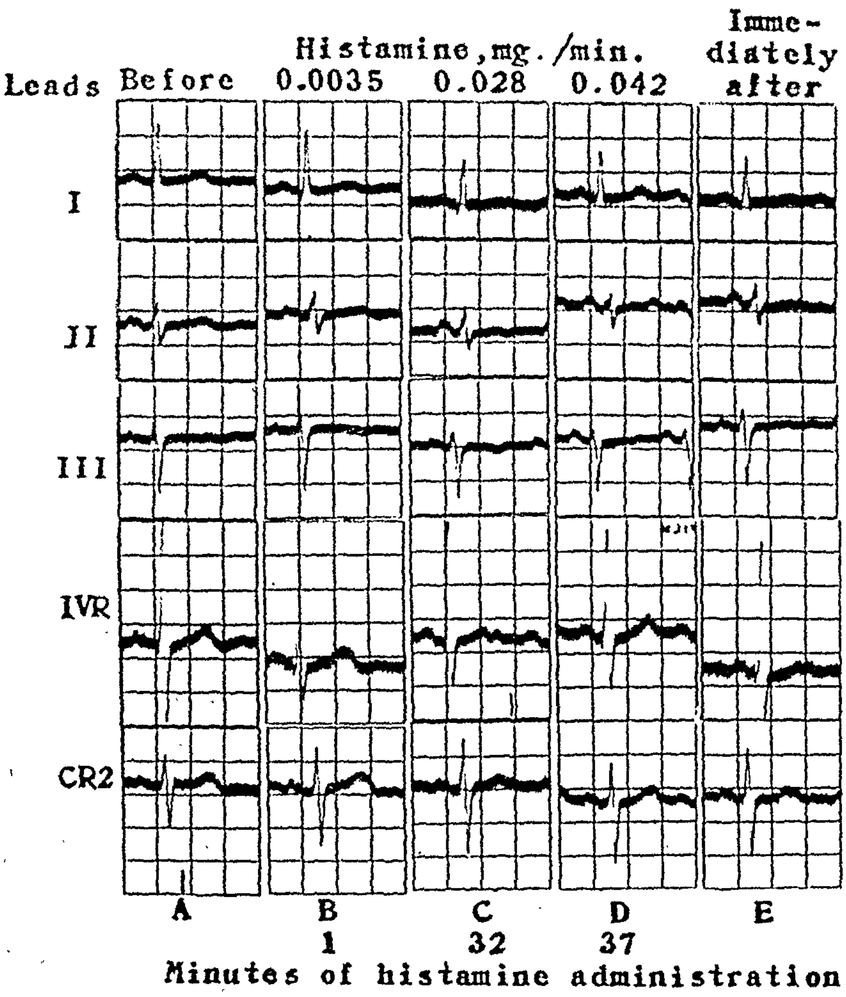

Fig. 2.—Electrocardiograms efbore, in the course of, and after administration of histamine. *A*, Control observation shows left axis deviation and isoelectric T wave in Lead III; *B*, T waves in Leads I and II are flattened slightly; *C*, T waves are isoelectric in Lead I, inverted in Leads II and III, and of lower amplitude in both chest leads; *D*, T waves have regained their amplitude in Lead I and some of their amplitude in both chest leads. In Lead III they are still slightly inverted; *E*, T waves in Leads I and II and both chest leads are flattened again.

appeared flattened again. On review of all of the electrocardiograms, it appeared as if the right side of the heart had become overburdened temporarily, as shown by the inverted T waves in Leads II and III, then had readjusted itself to the added strain in spite of the increased and continued dose of histamine. With the higher rates of injection of histamine, periods of overactivity of the heart, lasting three to four minutes, were observed with each increment of dosage. Also, the patient's respirations became more rapid and deep. Abnormal exchange of gas by hyperventilation, in addition to right ventricular strain, is a possible factor in the production of changes in the electrocardiograms.

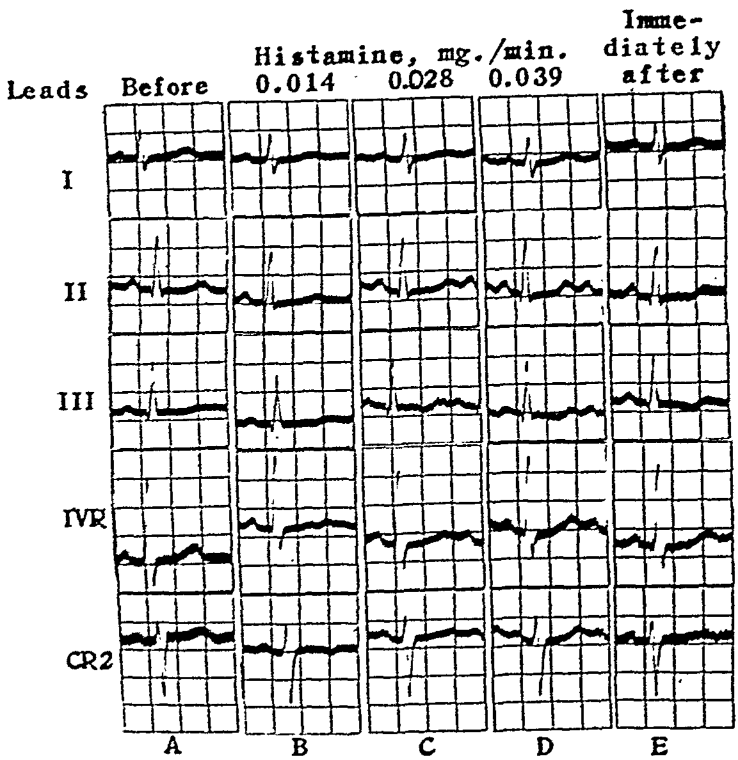

Fig. 3.—Electrocardiograms before, in the course of, and after administration of histamine. *A*, Control, showing isoelectric T waves in Lead III; *B*, T waves are decreased in all leads, flattened in Leads I and II, diphasic in Lead III, positive, but notched, in Lead IV R, and inverted in CR_2; *C*, T waves in Lead I and both chest leads are of low amplitude, and in Lead III are inverted; the inversion of the T wave in Lead CR_2 which was present in *B* has disappeared; *D*, T waves in Lead III are diphasic, and in both chest leads are increased in amplitude; *E*, T waves of all leads are of low amplitude; those in Lead CR_2 are most diminished.

Left axis deviation, in this case as well as in three others, remained unaltered throughout all of the tracings before, during, and after administration of histamine. Small Q waves were observed in Lead IVR at rates of administration of histamine base of from 0.009 to 0.028 mg. per minute.

In another case (Fig. 3), inversion of the T wave in Lead CR_2 and the presence of a notched, positive T wave in Lead IVR indicated right ventricular strain as well as in any of the cases studied. This case was the only one in which the T wave was inverted in any of the chest leads.

In the control electrocardiogram (Fig. 3, *A*), isoelectric T waves were noted in Lead III. When histamine was being given at the rate of 0.014 mg. per minute, the amplitude of the T waves was decreased in all leads, flattened in Leads I and II, diphasic in Lead III, and inverted in CR_2 (Fig. 3, *B*). The T wave in Lead IVR was a notched, positive wave. The maximal effect was observed when histamine base was being injected at the rate of 0.028 mg. per minute (Fig. 3, *C*). The T wave in Lead I at that time still exhibited low amplitude; in Lead III it was still inverted, but the inversion had disappeared in Lead CR_2. The T waves in both chest leads were still at low amplitude. When the rate of injection was 0.039 mg. of histamine base per minute (Fig. 3, *D*), the T wave in all leads regained considerable amplitude, and that in Lead III had become diphasic. Immediately after completion of the intravenous injection (Fig. 3 *E*), the T wave in Lead III became inverted again, whereas those in both chest leads lost what amplitude they had gained during the maximal rate of injection. In Lead I the T wave regained its original amplitude, but the remaining leads showed diminished voltage of the T waves. In this case the effect of histamine on the electrocardiogram was great, but the subjective and objective effects were slight. Electrocardiograms showed a Q-T time of 0.40 second in Lead II when the rate of administration of histamine was 0.039 mg. per minute; this is definitely prolonged when compared to the normals of Bazett. In the remaining twenty-two positive cases, similar, but less pronounced, electrocardiographic changes were exhibited.

Other Electrocardiographic Observations.—Premature ventricular contractions were observed after the administration of histamine in four cases. They usually developed when histamine was given at rapid rates, but in one case they disappeared at high rates, although they were present in all preliminary tracings. One patient had incomplete bundle branch block (QRS interval of 0.12 second) which was unknown to any of us until later. However, the incomplete bundle branch block did not change with the various rates of administration of histamine, nor did the patient appear to suffer in any way from the injection. Two and a half years later, electrocardiograms did not reveal any further change in this incomplete bundle branch block.

Notching of the P wave in Leads II and III disappeared in two cases during the injection of histamine. In three cases, however, diphasic P waves in Lead III, notched P waves in Leads II and III, and diphasic P waves in Leads I and III remained unchanged throughout all tracings. In one case the notched P wave returned after discontinuation of the injection of histamine. A P wave of low amplitude in Lead I became higher with increased flow of histamine in another case. In one case, the P waves in Leads II and III were notched occasionally during the administration of histamine. Notching and slurring of the QRS complex was not changed by histamine in thirteen cases. Notching was frequently observed in Lead III, and the slurring was about equally

distributed in Leads I, II, and III. Loss of voltage of the QRS complex was not striking nor consistently present. Diminution of the S wave in Lead IVR was observed in two cases. This effect appeared in both cases when histamine was being given at a rate of 0.0017 to 0.0035 mg. per minute, and continued until after the injection was completed.

Left axis deviation was encountered in six cases. It was present throughout all tracings in four cases, but in one it was found only immediately after administration of the drug was discontinued. In the remaining case, the slight left axis deviation which was present on the initial examination disappeared when the rate of histamine administration reached 0.022 mg. per minute. It had not reappeared approximately six minutes after discontinuation of injection of the drug. In this case also, premature ventricular contractions disappeared with high dosages of the drug. No cases of right axis deviation were encountered.

The T waves in Lead III which were already inverted in preliminary tracings were not deepened with increased amounts of histamine. In two cases the T waves in Lead III which were inverted became diphasic on increased rates of administration of histamine.

The cardiac rate was increased by the administration of histamine, as illustrated by Fig. 4. Little effect was noted until a rate of 0.013 and 0.015 mg. per minute was reached. Then, with each increment in dosage, there was a corresponding rise in cardiac rate. Sinus tachycardia was usually present with maximal administration. When the administration of the drug was stopped, the heart rate dropped back to its original, or to a lower, rate within five to ten minutes. The cardiac rhythm shifted back to either sinus rhythm or sinus bradycardia. The difference in the number of cases above the various rates of administration, as shown in Fig. 4, is explained by the fact that in some cases histamine was injected at different rates than in others. This was done because ability to tolerate the drug without headache varied. Some patients could take it rapidly, as if it were only physiologic salt solution, whereas others were more sensitive.

The electrocardiographic cycle was analyzed in order to find out what part of the cycle was affected. In thirteen cases during maximal injection of histamine there was an average decrease of 0.034 second in the P-R interval, as compared to the control period. In ten cases the P-R interval did not change, and in one case it increased temporarily. In this case the P-R interval increased from 0.20 to 0.24 second when the rate of administration of histamine increased from 0.0017 to 0.0158 mg. per minute. With increasing rates of injection, however, the P-R interval returned to its original length, namely, 0.20 second. In one other case the P-R interval was prolonged initially to 0.24 second. However, at rates of histamine injection from 0.021 to 0.044 mg. per minute, the P-R interval was reduced to between 0.20 and 0.22 second. Immediately after discontinuation of the injection of histamine the P-R

interval returned to its former length of 0.24 second. Failure to observe impairment of auriculoventricular conduction, as reported by other investigators, may have been due to the relatively smaller amounts of histamine used. There was no effect on the QRS interval. The S-T interval decreased in twelve cases, remained unchanged in ten, and increased in three. The average decrease in time was approximately 0.05 second. The average increase was 0.027 second. The Q-T time was observed to be prolonged in eight cases when the cardiac rate was elevated by the histamine, that is, the Q-T interval remained what it was originally, and did not decrease with the increase in cardiac rate. Compared to the normal values of Bazett, the average decrease in Q-T time would have been 0.072 second, but actually the average was 0.0075 second. The T-P interval, of course, showed an inverse proportion to the increase in cardiac rate, and was reduced to zero in some cases.

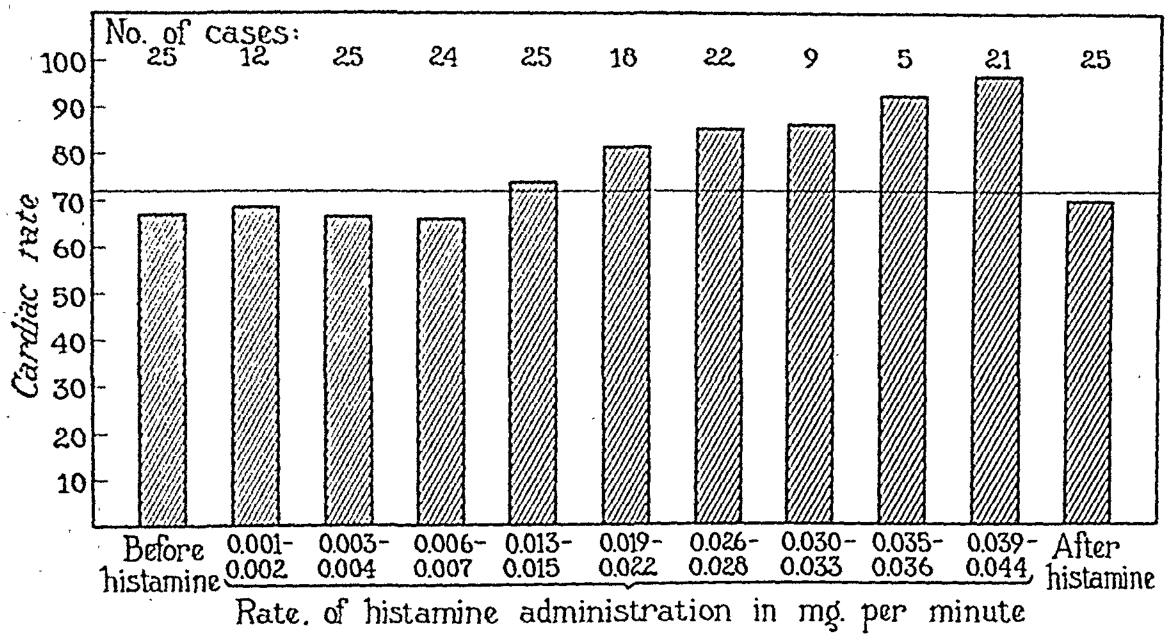

Fig. 4.—Increase in heart rate in proportion to rate of administration and dose of histamine.

COMMENT

To explain how histamine causes the T wave to lose amplitude and become inverted is a difficult undertaking, for it involves the theory of electrocardiography and the mechanism of formation of the T wave, concerning which investigators are not all agreed. Therefore, although an attempt on our part to explain this effect on the T wave may appear presumptive, it is done only for the purpose of presenting what seems to be the most plausible explanation in the light of the present investigation.

Several possibilities may be considered in regard to the manner in which histamine produces its effect on the T wave. The first is whether the amine produces coronary vasoconstriction and thereby brings about myocardial ischemia. There are several pieces of evidence against this explanation, for such experimental work as that of Essex, Wegria, Herrick, and Mann[6] on the trained dog and the work of Anrep[7] on the heart-

lung preparation of human beings demonstrate that histamine produces coronary vasodilatation in these species. Moreover, in the twenty-five cases investigated and many others not included in our study, neither anginal distress nor signs of coronary insufficiency were encountered. Also, if anoxemia were produced, the electrocardiographic changes which are characteristic of this condition, as shown by Levy, Bruenn, and Russell,[8] would be expected. Inversion of the T waves in Leads I and IVR was never encountered, nor was the RS-T junction displaced, as they reported. Loss of voltage in the QRS complex was not observed, either. However, Levy, Bruenn, and Russell[8] mentioned that, in normal persons during induced anoxemia, the T waves tended to lose amplitude in all four leads, and inversion of the T waves in Leads II and III occasionally occurred. Rothschild and Kissin[9] pointed out that the alterations of the electrocardiograms in anoxia disappear slowly, and persist in diminishing degrees in some instances for as long as thirty minutes. The work of Levy and his associates and of Rothschild and Kissin is of particular importance because it demonstrates that the electrocardiographic changes caused by anoxia, although they are similar in some respects to those produced by histamine, are, in the main, different.

The next question is whether histamine produces its effect on the T wave through the vagus nerve. Stimulation of the vagus has been shown to produce T waves of low amplitude by Samojloff,[10] Rothberger and Winterberg,[11] and Kronenberger and Ruffin.[12] This question can be answered in the negative if the work of Hashimoto,[13] who sectioned the vagal nerves of dogs and also gave large enough doses of atropine to paralyze the vagal nerves, is accepted. He found that the effect of histamine on the heart was not prevented by such procedures, and concluded that the action of histamine was mediated in some other manner. Moreover, histamine always produces acceleration of the heart, which is not a characteristic of vagal activity.

Whether histamine produces its effect on the T wave through the sympathetic nervous system must also be considered. This is hardly likely, for stimulation of the accelerator nerves, as shown by various investigators,[10-12] the use of epinephrine, and conditions, such as hypoglycemia, which cause an increased outflow of epinephrine, have produced larger than normal T waves.

The next question to be considered is whether the amine acts directly on the myocardium as a toxic agent. If this were true, the faster histamine is administered, the more pronounced would be the loss of amplitude of the T wave and the deeper the inversion. This is not entirely true. In several cases the amplitude of the T wave returned to normal in spite of continued and increased administration of histamine. However, histamine may act directly on the myocardium.

The most likely explanation of the T wave negativity is that it reflects right ventricular strain, although tachycardia and hyperventila-

tion may be additional factors. Although the electrocardiographic changes do not resemble those in pulmonary embolism exactly, because there is no prolongation of the Q wave in Lead III or incidence of right axis deviation, in one case the T wave was inverted in Lead CR_2 and was notched and positive in Lead IVR. This probably represents the maximal effect of histamine in producing right ventricular preponderance, for, in the other cases, the effect was much less pronounced. Dale and Laidlaw[14] reported that large intravenous injections of histamine produced transient distention of the right side of the heart, with weak right ventricular contractions, in cats which were given artificial respiration while the thorax was open. Also, Kirch[15] reported that, in the dog, cat, rabbit, and guinea pig, a definite tonogenic dilatation of the right ventricle occurred when histamine was injected into the veins and heart. Daily injections produced a definite right-sided hypertrophy of the heart in the dog and cat. This was believed to be due to an increase in the blood pressure in the pulmonary circulation, caused by contraction of the small pulmonary veins, aided by spasm of the bronchial musculature. The results of our investigation bear out the possibility that increased intrapulmonic pressure is responsible for the electrocardiographic changes, as shown by the preponderance of inversion of the T waves in Leads II and III, as well as the case in which the T wave was inverted in Lead CR_2, with a positive, notched T wave in Lead IVR. These changes point to right ventricular strain as probably the most plausible answer.

The effect of histamine was not prolonged, which indicates that it was being quickly neutralized or destroyed in the blood stream. Prolongation of the conduction time was found in only one case. In most of the cases the conduction time, contrary to experimental reports in the literature, was decreased. As a whole, the electrocardiographic changes did not appear remarkably significant, and were of a transient and physiologic nature. Experimental work which substantiates this opinion is that of Ettinger, Hall, and Lang,[16] who gave dogs histamine intravenously daily for as long as 266 days. The concentration of the histamine solution was 1:10,000, and 2 to 4 c.c. were given per minute for ninety minutes daily; this was enough to double or triple the heart rate. Post-mortem examinations revealed no evidence of degenerative changes in the coronary arteries or myocardium after the conclusion of the experiment. In our experience, histamine has never precipitated an attack of angina pectoris or coronary occlusion, either in the twenty-five cases studied or in many hundred other cases in which histamine was given intravenously. From this it might be inferred that histamine does not produce coronary vasoconstriction.

In the concentration used, and under the conditions set forth in this paper, the electrocardiographic changes induced by histamine appear to be physiologic and relatively unimportant. Therapeutically, the importance of such a conclusion is evident, but a word of warning should

be voiced for patients who have chronic asthma, for they are notoriously sensitive to histamine.

SUMMARY AND CONCLUSIONS

Electrocardiograms were made on twenty-five human subjects: seven women and eighteen men who did not have cardiac disease. These electrocardiograms were made before, in the course of, and after the continuous intravenous administration of 2.75 mg. of histamine diphosphate in 250 c.c. of physiologic salt solution at rates varying from 0.0017 to 0.044 mg. per minute. Physiologic salt solution was given intravenously to three patients in the same manner as histamine diphosphate, and did not have any effect on the electrocardiograms in any of the four standard leads. Electrocardiograms were taken with the usual three leads in eight cases, and with the aid of Leads CR_2 and IVR in the remaining seventeen cases.

Age and concentration of serum potassium appeared to play little, if any, role in the electrocardiographic changes which occurred after the intravenous use of histamine.

Significant changes were observed in the electrocardiograms in twenty-four of the twenty-five cases (96 per cent). The most common change was loss of amplitude of the T waves in different leads, sometimes in all leads, which, in some cases, proceeded to either the isoelectric level or to inversion of the wave. The first effect appeared most frequently in Lead III, next in Lead II, then in Lead CR_2, Lead I, and finally in Lead IVR. Inversion of the T waves was observed in four cases in Lead II, in nine cases in Lead III, and in one case in Lead CR_2. No inversion was observed in Leads I and IVR. The effect of histamine on the T waves disappeared within five to fifteen minutes after injection of the drug was discontinued. The extent of loss of T-wave voltage was roughly and directly parallel to the rate of administration of histamine. In some cases, however, the effect of histamine was lost, and the T waves recovered either partially or completely their former amplitude in spite of a continued and sometimes increased dosage of histamine.

The cardiac rate was increased, on an average, 26 beats per minute by the administration of histamine. The average rate before injection was 68 beats per minute, and, during maximal injection of histamine, 94 beats per minute. The cardiac rhythm was also affected; the initial rhythm was usually sinus arrhythmia, sinus bradycardia, or sinus rhythm, which shifted to sinus tachycardia during maximal rates of injection.

Impairment in atrioventricular conduction was manifest in only one case, and this was for only a short time during the early stages of the injection of histamine. In all other cases the P-R interval or the conduction time decreased. In one case of incomplete bundle branch block, no further impairment in conduction followed the use of histamine.

Premature ventricular contractions were observed after the administration of histamine in four cases. They usually developed during high rates of injection. Flattening of the QRS complex was not striking nor consistently present.

Left axis deviation was observed in six cases and was present throughout all tracings in four cases. In one of the other two cases, left ventricular preponderance appeared after the injection of histamine, and in the other, disappeared with increased doses of histamine. Right axis deviation was not encountered.

Electrocardiographically, the effects of administering histamine intravenously in man, in the manner described, may be considered of minor physiologic importance. No clinical or electrocardiographic evidence of permanent cardiac damage was observed in any of the twenty-five patients. No anginal distress or definite symptoms of coronary insufficiency were observed.

The authors wish to thank Dr. A. R. Barnes for criticism and suggestions.

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Clinical Report

BALL THROMBUS IN THE RIGHT AURICLE OF THE HEART, WITH A DESCRIPTION OF THE SYMPTOMS PRODUCED

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A CASE of ball thrombus of the right auricle of the heart is reported for the following reasons:

1. A review of the literature revealed only thirty-five authentic cases of ball thrombus of the heart. In thirty-four of these the ball thrombus was found in the *left* auricle. The single exception was found in the right ventricle.[1] The case herein presented, therefore, represents the first reported instance in which an unquestionable ball thrombus occurred in the right auricle.

2. The presence of the large, freely movable ball in the right auricle produced an unusual syndrome that may lead to a consideration of this possibility in other cases. The diagnosis of a ball thrombus of the left side of the heart has been rarely made or even suggested ante mortem. So far as we can ascertain, it has never been made and confirmed in relationship to the right auricle. In this case an unusual series of findings made it possible to deduce that a movable thrombus was acting as a ball valve over the tricuspid orifice, although it could not be ascertained whether it was loosely attached or entirely free.

3. Lastly, the ball thrombus was of unusual size, measuring 6.8 cm. in diameter, whereas, in the previously reported cases, the thrombi varied from 1 to 4 cm.

Certain criteria, set down by Welch, in 1899,[2] have been generally acknowledged as necessary of fulfillment before the anatomic diagnosis of a ball thrombus can be accepted. There must be (a) entire absence of attachment, with consequent free mobility, (b) imprisonment in consequence of excess in diameter of the thrombus over that of the first narrowing in the circulatory passage ahead of it, (c) such consistency and shape that the thrombus must not of necessity lodge as an embolus in this passage. Our case clearly fulfills these specifications.

No attempt will be made to review all of the reported cases of ball thrombus of the heart. The first case reported, a ball thrombus in the left auricle, was described by William Wood, of Edinburgh, in 1814.[3] Nearly seventy years later, von Recklinghausen[4] described his cases.

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Received for publication Oct. 22, 1943.

He is nevertheless frequently referred to in the German literature as the original observer of this phenomenon. Abramson[5] ably reviewed the literature up to 1924. Since that time others have added cases.[6-15]

Only a single case in the literature needs to be considered in relation to the one here presented. This was reported by MacLeod, in 1882.[16] Recklinghausen,[4] Strange,[17] and Abramson[5] concluded that this case should not be admitted to the class of ball thrombi. While the possibility that MacLeod did find a true ball thrombus does exist, it cannot be clearly so classified from his report because of failure to describe certain essential structural features. These are: the presence or absence of a pedicle, the exact shape of the "clot," and its size relative to that of the tricuspid orifice. MacLeod's exact description was as follows: "In the right auricle was a very firm almost cartilagenous grayish yellow, movable clot, half as large again as a walnut lying over the tricuspid orifice."

Extreme air hunger in the absence of any evidence of interference with the air passages, and with free expansion of the chest, together with periodic unconsciousness and a very thready pulse, led MacLeod to conclude that "there was some interference with the afflux of blood to the lung. The signs and suddenness of the attack pointed to a large embolic plug in the lesser circulation somewhere near the right side of the heart and probably in the pulmonary artery." These deductions did not include the possibility of a ball thrombus in the right side of the heart.

REPORT OF CASE

The patient, a 47-year-old, white, married man, was admitted Jan. 7, 1943, to the Army and Navy General Hospital because of acute heart failure. He had been in good health until the age of 23 years (1919), when he fainted several times while taking exercises. He stated that he was discharged from the Army because of these fainting spells. From that time he experienced increasingly severe dyspnea, as well as subjective evidences of cardiac insufficiency on exertion. On Aug. 4, 1939, he was hospitalized because of signs of a mild degree of cardiac decompensation; this quickly cleared up, and he left the hospital in relatively good health. On Aug. 18, 1942, he experienced his first definite and severe attack of cardiac decompensation. He was then hospitalized, and had severe dyspnea, cough, abdominal swelling, and edema of the ankles. The diagnosis made at that time, according to his statement, was "valvular heart disease." No irregularity in cardiac rhythm was noted. He responded to rest in bed and digitalization with marked improvement. A chest roentgenogram, taken Aug. 28, 1942, revealed an enlarged heart, with marked prominence of the right auricular border (Fig. 1). He left the hospital Sept. 26, 1942, but returned Oct. 6, 1942, with a second severe break in compensation. While at home he had failed to maintain digitalization and had consistently exceeded his exercise tolerance. During this admission he came under the observation of the present authors. This attack was characterized by the following symptoms: severe dyspnea, with orthopnea, severe precordial pain, cough, nausea, oliguria, and weakness. Physical examination revealed an acutely distressed, dyspneic patient with a dusky purplish cyanosis

of the face. The veins of the neck were engorged and actively pulsating. The timing of this pulsation was difficult. Diffuse, fine, persistent, crepitant râles were heard posteriorly over the bases of both lungs. These were not moist. The heart was enlarged, on percussion, to the left anterior axillary line in the sixth intercostal space. In this area a diffuse apical pulsation was visible and palpable. The right side of the heart extended approximately 6 cm. to the right of the midsternal line at the same level. The base was not widened. The rhythm was totally irregular. This was interpreted as due to auricular fibrillation, which was confirmed by the electrocardiogram. Rough systolic and soft blowing diastolic murmurs were heard, and were loudest over the mitral area. These were audible from the right border of the sternum to the left apex. The abdomen appeared to be enlarged due to moderate ascites. There was a large tender liver that extended 4 fingerbreadths below the costal margin. The liver pulsated synchronously with the ventricular systole. There was moderate edema of the ankles. Roentgenograms taken during this admission showed essentially the same picture of the heart as that seen during the first admission. Other laboratory data were essentially irrelevant.

The patient again responded rather remarkably to rest in bed and digitalization. His symptoms were definitely improved, although his auricular fibrillation continued and his exercise tolerance remained very limited (e.g., walking slowly across a room). The cyanosis, as well as the engorgement and pulsation of the veins of the neck, was markedly lessened. The liver decreased in size to within normal limits and ceased to pulsate. He left the hospital on Nov. 14, 1942, against medical advice. The diagnoses at the time of discharge from his second admission were as follows:

1. Rheumatic fever, inactive.
2. Myocardial degeneration with insufficiency, secondary to No. 1.
3. Mitral stenosis and insufficiency, secondary to No. 1.
4. Tricuspid insufficiency, secondary to No. 1 and No. 3 (possible tricuspid stenosis?).
5. Cardiac hypertrophy and dilatation affecting all chambers, secondary to No. 1, No. 2, No. 3, and No. 4.
6. Cardiac arrhythmia, severe, chronic, with auricular fibrillation and ventricular premature contractions, secondary to No. 1 and No. 2.

He was advised to continue a maintenance dose of digitalis, but his personal physician discontinued this and replaced it with strychnine. When he became more decompensated, digitalis was again used, but it was rather irregularly taken, and he had none during the two days prior to his final admission on Jan. 7, 1943. On this admission he was again in an extreme state of decompensation. The symptoms and signs were essentially as they were on the second admission. Nausea, dyspnea, orthopnea, ascites, and oliguria were, however, somewhat more prominent than previously. The dyspnea appeared to be of an oxygen hunger type, and not due to respiratory obstruction or congestion. There was no pain in the chest. He gave the history that, on several occasions during the preceding month, his left leg became limp when he tried to walk. This was not accompanied by pain or swelling of the leg.

On his last admission (Jan. 7, 1943) the physical signs relating to the heart were as follows: There was a diffuse visible pulsation in the

area of the fifth and sixth intercostal spaces and at the left anterior axillary line. The rhythm was still totally irregular—the apical rate approximated 140 per minute, with a deficit at the radial artery of 10 to 20 beats. The rough systolic and soft, blowing, diastolic murmurs above described were heard from the right border of the sternum to the left axilla at the level of the sixth intercostal space. They appeared to be loudest to the left of the sternum. The dusky cyanosis of the face and neck was pronounced, and systolic pulsations of the cervical veins and of the markedly enlarged liver were very striking. The right sub-

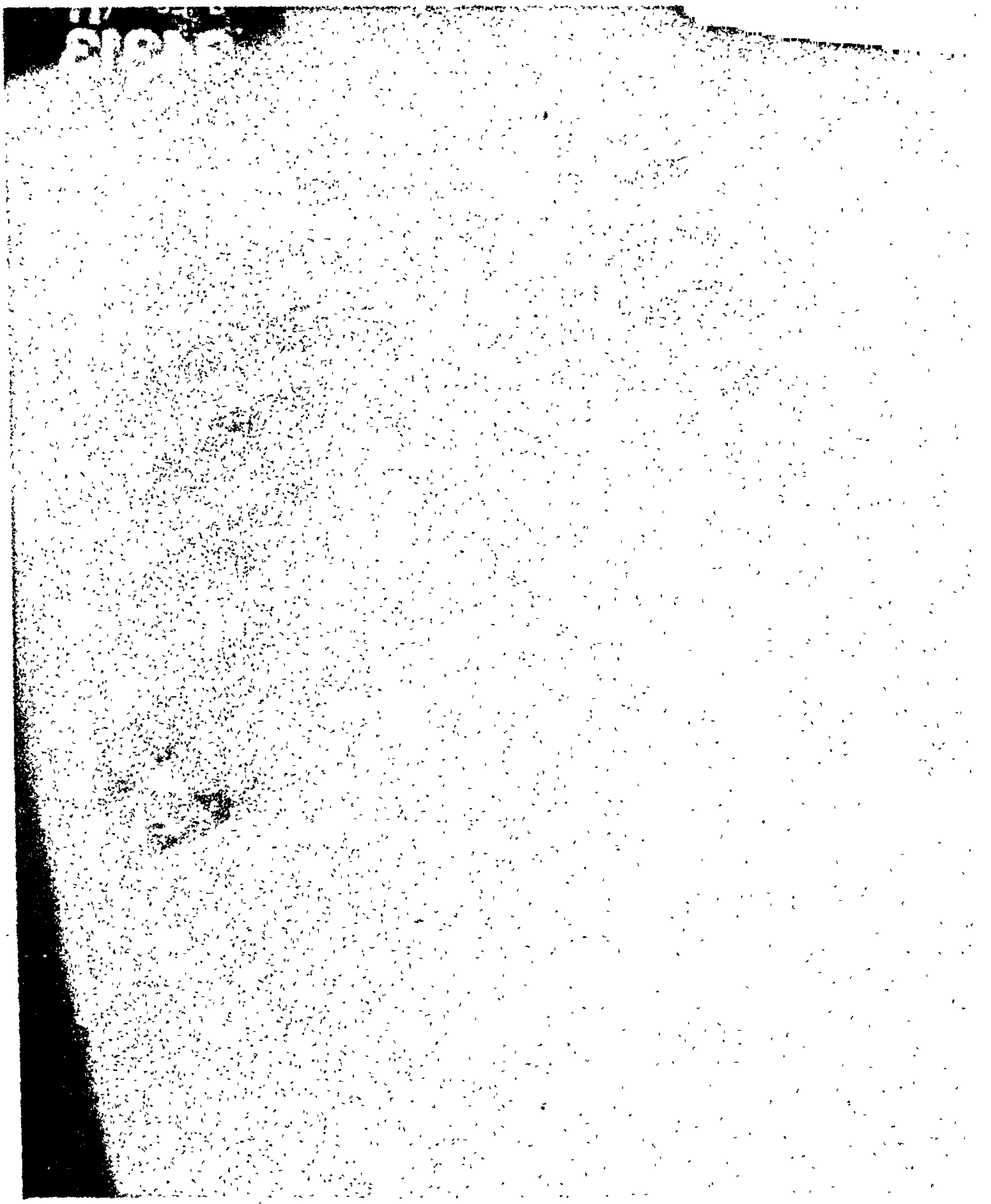


Fig. 1.—Roentgenogram of chest taken Aug. 28, 1942, showing marked generalized enlargement of the heart, with especial prominence of the right auricular area.

clavian vein was distended, showing behind and above the right clavicle. At times, during an acute attack, the saphenous veins were noted to pulsate, but this was not constant. Slight pretibial edema was present, and he had generalized peripheral arteriosclerosis.

Laboratory Data.—On admission the urine had a specific gravity of 1.015. It contained no sugar, but 1 plus albuminuria was present. Microscopically, 10 to 15 leucocytes and a few hyaline and granular casts per high-power field were seen. Increased amounts of albumin and hyaline and granular casts were noted terminally. The blood Kahn

TABLE I

LABORATORY STUDIES

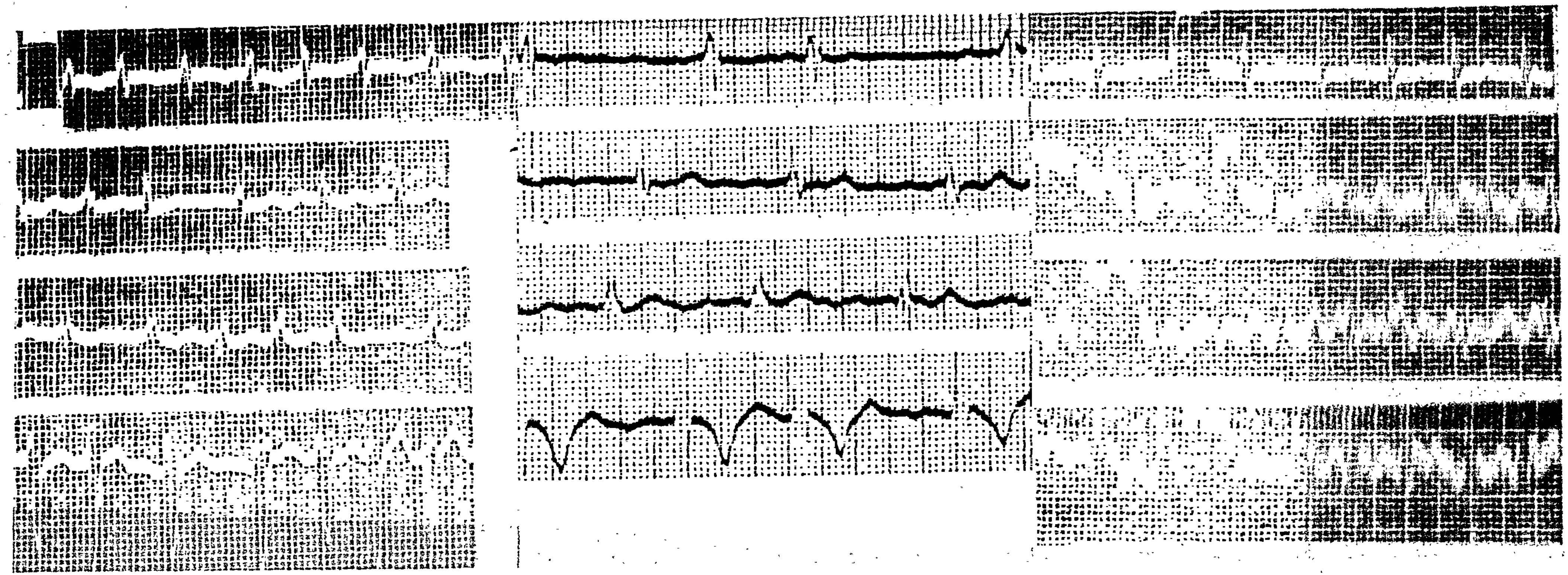
	1/11/43	1/14/43	1/18/43	2/25/43
Blood Nonprotein Nitrogen	85 mg. %	76 mg. %	42 mg. %	300 mg. %
Blood Creatinine	3.15	3.0	2.27	5.0
Blood Sugar	142.8		83.3	222.0
Blood chlorides				672.0

	1/9/43	1/15/43	2/25/43
R.B.C.	3,930,000	4,610,000	4,710,000
W.B.C.	15,300	7,200	50,000
Hgb.	80%	95%	98%
Polymorphs	82%	76%	88%
Lymphocytes	18%	24%	12%
Polychromatophilia			
Occasional normoblasts			

test was negative. An electrocardiogram taken on admission, Jan. 7, 1943, showed auricular fibrillation with a ventricular rate of 140, with slurred QRS complexes of low amplitude in Leads I, II, and III. A diphasic T_2 and inverted T waves in Lead III were noted. There was no evidence of a digitalis effect (Fig. 2*A*).

Hospital Course.—He was immediately put to bed and given sedatives, ammonium chloride, theobromine, and digitalis, and his fluid intake was restricted to 1,200 c.c. daily. The blood pressure was approximately 100/90. During the next forty-eight hours his condition became progressively worse; nausea and vomiting permitted the use of only parenteral medication and feeding. Oxygen was administered continuously through a catheter in the nose, and 2 c.c. of mercupurin were given. The ventricular rate varied between 140 and 160. By the third day (Jan. 10, 1943), his condition had improved slightly. His ventricular rate had slowed to 95 and the electrocardiogram showed early evidence of a digitalis effect. He appeared more comfortable. The liver had receded from 4 to 2 fingerbreadths below the costal margin. His fluid output had markedly increased, but unfortunately was not recorded. The following day (Jan. 11, 1943), his general condition was further improved. The edge of the liver was barely palpable, and the hepatic and venous pulsations were markedly reduced. The patient appeared somewhat drowsy and slightly dehydrated, so that his fluid intake was increased to 1,500 c.c. The administration of oxygen by nasal catheter was continued. The ventricular rate averaged between 90 and 100. From this time, digitalization was maintained by the use of 1½ grains (0.1 Gm.) once or twice a day. This was occasionally supplemented by one ampoule of digifoline. The condition of the patient, evidence of failure, ventricular rate, and frequent electrocardiographic records determined the dosage.

On Jan. 12 he was still drowsy and unaware of his surroundings. The most striking change was the disappearance of all abnormal venous pulsation. The edge of the liver was no longer palpable. The blood pressure was 110/70. The ascites and edema had disappeared. Oxygen was still being administered continuously. The next day (January 13) he appeared much better, and was fairly alert for the first time. The liver was not palpable and the abnormal venous pulsations were still absent. The ventricular rate was approximately 100. The cardiac rhythm was auricular fibrillation, with a few ventricular premature contractions. On January 14 the patient appeared further improved.



A.

B.

C.

Fig. 2*A*.—Jan. 7, 1943. Ventricular rate about 140. Auricular fibrillation. QRS complexes 0.08 second duration. QRS slurred and notched, all leads. Diphasic T_1, and negative T waves, Lead III. No digitalis effects.

Fig. 2*B*.—Jan. 19, 1943. Ventricular rate 68. Auricular fibrillation. QRS complexes 0.12 second duration. QRS complexes slurred and notched. Diphasic T waves, Lead I; inverted T waves, Lead V_1.

Fig. 2*C*.—Feb. 25, 1943 (patient in extremis). Ventricular rate about 150. Auricular fibrillation. QRS complexes 0.08 second duration. RS-T segments depressed, Lead I; diphasic T waves, Lead I.

He was no longer cyanotic, and oxygen was discontinued. During the next nine days he made slow but steady progress. His heart remained quite well compensated on a dose of 0.1 Gm. of digitalis daily. His cardiac rate averaged about 66 (Fig. 2*B*). His mental condition was now good. His blood pressure averaged 100/70. Within twenty-four hours, however (Jan. 27, 1943), and without any change in the treatment, he again showed evidence of tricuspid insufficiency. The liver once more became markedly enlarged and pulsatile, and the veins of the neck engorged. The ventricular rate suddenly dropped to 46. The possibility of overdigitalization was considered, and the dose was reduced to 0.032 Gm. (½ grain) daily. Mercupurin (1 ampoule) was given parenterally. Once more, over a period of seven days, his condition showed steady improvement. He felt much better, but the signs of tricuspid insufficiency remained (pulsating liver and veins, and cyanosis). This relatively comfortable phase continued another week, until Feb. 14, 1943, when he apparently had an acute cerebral accident. He developed flaccid paralysis of the entire left side of the body. The head, neck, mouth, and eyes were drawn to the right. The blood pressure was approximately 150/80-60. The next day (Feb. 15, 1943), flaccid paralysis of the left side was still present. A Babinski sign had developed on the left side, but there was none on the right. The asymmetry of the face was less marked. He could hold his head more toward the midline. The tongue could be held nearly straight. The eyes, however, could not be rotated to the left. He reacted to abdominal palpation as if he had generalized pain. At this time the liver and neck veins had again receded, and there was no shortness of breath. It was believed that he had probably had a cerebral embolism from a left auricular thrombus. During the next ten days there was very little change in the neurological signs. Fever developed on February 20, and the temperature reached 105° F. Sulfathiazole was given, and the temperature returned to normal, but rose again to 102° F. terminally. The evidences of tricuspid insufficiency again returned to a marked degree and increased steadily until Feb. 24, 1943, when they reached a maximum; scattered coarse râles were heard throughout the bases of both lungs. A roentgenogram of the chest taken at that time showed evidence of moderate pulmonary congestion and marked enlargement of the heart to the left and to the right, with prominence of the right auricular border (Fig. 3). This was not remarkably different from the one taken Aug. 28, 1942 (Fig. 1). Within twenty-four hours, however, a very striking phenomenon took place. As shown in Fig. 4, the roentgenogram taken February 25 showed a marked reduction in the total size of the heart. Especially noteworthy was the total disappearance of the right border behind the sternal shadow. This was once more accompanied by a disappearance of the liver under the costal margin, and absence of abnormal pulsations of the cervical veins. This series of rapid changes in the severity of the tricuspid syndrome, together with the sudden reduction in the size of the right side of the heart, led the clinicians to conclude that a large thrombus must be riding over the tricuspid valve and exerting a ball valve action. There was no way of determining whether it was attached by a pedicle or was a free, ball thrombus. In either case the action could be the same.

On Feb. 26, 1943, the patient became much worse. The skin and sclerae became a dusky yellow as well as cyanotic; the cyanosis was more pronounced on the paralyzed side (left). The skin was cold and dry, and numerous petechiae appeared above the umbilicus and in

Fig. 3.—Roentgenogram of chest taken Feb. 24, 1943, showing little change from that of Aug. 28, 1943, except for slight increase in size. The prominence of the right border is still present.

Fig. 4.—Roentgenogram of chest taken February 25, 1943 (twenty-four hours later). Note the marked reduction in the total size of the heart shadow, and especially the disappearance of the right auricular shadow behind the sterum.

scattered areas down the right leg. No difference in the peripheral pulsations on the right and left sides could be detected. The blood pressure was approximately 170/40-45, i.e., there was a marked increase in pulse pressure. The pulse was totally irregular and feeble, and the ventricular rate averaged 150. An electrocardiogram taken at this time is shown in Fig. 2C. Râles and rhonchi were heard throughout the chest. The abdomen was scaphoid without rigidity. Neither the liver nor spleen was palpable. The cervical veins showed no abnormal pulsations. The left-sided hemiplegia remained flaccid, but clonus involving the right arm and foot developed. A urea frost was noted over the face and trunk.

The nonprotein nitrogen rose at that time to 300 mg. per cent, with a creatinine of 5 mg. per cent; the blood sugar was 220 mg. per cent, and the chlorides, 672 mg. per cent. The blood cell count was essentially normal except for a terminal rise in the leucocytes to 50,000. Neither hematuria nor melena was noted at any time, although the observations were carefully checked. He died at 7:45 P.M.

Autopsy.—At autopsy the diagnoses were as follows: (1) Stenosis, mitral, severe. (2) Valvulitis, fibroblastic, aortic valve, ancient. (3) Endocarditis, verrucous, rheumatic; mitral valve and left auricle. (4) Thrombus, ball (diameter, 6.8 cm.), right auricle. (5) Thrombus, mural, left auricular appendage. (6) Hypertrophy and dilatation, right ventricle. (7) Dilatation, left and right auricles. (8) Pneumonia, confluent lobular, early. (9) Congestion, chronic, passive. lungs. (10) Emboli, thrombotic, mesenteric artery, secondary to mural thrombus, left auricle; old and recent. (11) Infarction, ileum, secondary to occlusion of mesenteric artery. (12) Peritonitis, generalized, secondary to infarction of intestine. (13) Infarction, spleen, moderately large, secondary to mural thrombus, left auricle. (14) Abscess, subdiaphragmatic, secondary to generalized peritonitis. (15) Abscess, spleen, at site of infarction, secondary to subdiaphragmatic abscess. (16) Encephalomalacia, right internal capsule, secondary to embolism arising from left auricle. (17) Hemorrhages, pontine. (18) Uremia (clinical). (19) Pericarditis, secondary to uremia, localized. (20) Frost, uremic, face and trunk. (21) Cirrhosis, cardiac type, moderately advanced. (22) Icterus, secondary to cardiac cirrhosis. (23) Proctitis, hemorrhagic, probably secondary to uremia. (24) Infarctions, left kidney, small, secondary to emboli arising from mural thrombus, left auricle.

Only the heart is described in detail. In situ the heart was moderately enlarged. Its greatest transverse diameter measured 15 cm. The shape was globular because of marked dilatation. The apex of the heart was located at the sixth rib. The epicardium near the pulmonary conus contained some fibrin; this was not conspicuous, however. The left auricle was markedly dilated, and had slightly displaced the esophagus to the right and exaggerated the tracheobronchial angle. A large, firm tumor could be palpated through the dilated right auricle. The coronary arteries were patent. They were of normal caliber and collapsed readily on section. Dissection of the heart revealed a large, smooth-surfaced yellowish mass in the right auricle. The mass was spherical and free to move, for it was not attached in any manner to the wall of the auricle. There was no evidence of a former pedicle. The diameter of the ball thrombus was 6.8 cm., and the circumference was 21.4 cm. The thrombus had considerably reduced the capacity of the auricle, and, in fact, it was difficult to see how much blood could have entered this chamber. Sections through the thrombus revealed

various hues of gray and red, with slight central softening. The endocardium of the right auricle and right ventricle was everywhere smooth any shiny. The tricuspid valve was markedly stretched, with a circumference of 14.5 cm. It was delicate and of tissue paper thinness. The papillary muscles of the right ventricle were thickened and somewhat shortened, and there was widening of the interpapillary spaces. The myocardium of the right ventricle measured 4 mm. in thickness. The left auricular appendage contained a dry, friable, inelastic mass of tissue which could be easily torn away except at its base. This mass of tissue measured 3 cm. in length. The free extremity of the mass was roughened, as if a portion had recently broken away. The anterior and posterior aspects of the wall of the left auricle were studded with small, reddish-pink, firm, globular, verrucous lesions. None of the verrucous lesions measured over 3 mm. in height. They were intimately adherent to the wall and could not be removed except at the expense of the endocardium. When removed, they left a raw surface. There were three plaques of these lesions. They covered an area of approximately 2 cm. each. The endocardium of the left ventricle was smooth and shiny. The pulmonary valve was delicate and of tissue paper thinness. The circumference of the mitral valve was, however, markedly reduced by fusion of the individual leaflets. The fusion of the leaflets prevented flattening out of the left ventricle when the valve was sectioned. The opening of the intact valve admitted only the tip of the index finger. It measured not over 1 cm. in diameter. The fused leaflets were markedly puckered and rigid. At the free margin the valve measured 4.5 mm. in thickness. A few millimeters from the valve margin there were numerous small, reddish-pink, verrucous lesions similar to those on the endocardium of the left auricle. Again, none of the lesions were friable, but they were moderately firm and difficult to remove. The chordae tendineae were noticeably shortened and appreciably thickened. The aortic leaflets were distinct, but were stiffened, and the margins were slightly puckered and thickened. The circumference of the valve was slightly reduced. No verrucous lesions were present on the aortic valve. The tricuspid valve was normal except for dilatation.

Microscopically, the right auricular tissue was normal. The tricuspid valve was likewise normal. The ball thrombus consisted of concentric layers of fibrin and platelets, with scattered erythrocytes and a few leucocytes. No Aschoff nodules were found in the myocardium of the right ventricle. Two pieces of the mitral valve were studied. The free margins of both were extensively thickened by connective tissue, much of which was hyalinized. At a slight distance from the end of the valve the superior surface was covered by fibrin masses that were attached to the valve by a single broad pedicle. Near the attached margins the underlying tissue was infiltrated by inflammatory cells consisting chiefly of lymphocytes, a few large mononuclears, and an occasional polymorphonuclear leucocyte. Throughout the area of infiltration by inflammatory cells there were scattered vascular spaces, some of which had relatively thick walls. The distal extremity of the aortic valve was thickened by hyalinized connective tissue. Only a few clusters of lymphocytes were seen near the outer margin. The sections of the left auricle showed that a portion of the endocardium was considerably thickened by connective tissue. On the outer surface of the thickened endocardium there was an irregular layer of fibrin, in the interstices of which were lymphocytes, large mononuclears, and a few plasma cells. This irregular layer corresponded to the vegetations described grossly.

In the epicardium of one section there was a zone of hemorrhage. In the myocardium subjacent to the vegetations, many of the fibers were separated for slightly greater distances than normal by connective tissue. No Aschoff nodules were noted. Two sections of the left auricular appendage were studied microscopically. Both contained a portion of the mural thrombus described grossly.

COMMENT AND SUMMARY

A case of ball thrombus in the right auricle of the heart is presented for the following reasons: (a) It is the first reported case of unquestionable ball thrombus in the right auricle; (b) it satisfies all of the criteria laid down by Welch for a true ball thrombus; (c) it produced a syndrome which, if encountered again, seems sufficiently characteristic to warrant consideration of a diagnosis of a thrombus acting as a ball valve mechanism over the tricuspid valve; (d) this possibility was suggested in the present case before death (it is not believed possible to ascertain before death whether or not the clot is attached by a pedicle); (e) this ball thrombus was of unusual size, i.e., 6.8 cm. in diameter; those previously reported varied from 1 to 4 cm. in diameter.

The syndrome which should lead to a consideration of ball thrombus (or other freely movable thrombus) in the right auricle includes the following: (1) Dusky cyanosis of the face and neck; (2) engorgement of the veins of the neck, with a systolic pulsation. This is even more significant if other veins, such as those of the arms and legs, show engorgement or a systolic pulsation; (3) marked dyspnea of oxygen hunger type, without adequate explanation in the form of difficulty in respiratory movement, obstruction, or congestion of the respiratory passages or lungs; (4) marked enlargement of the right side of the heart, especially the right auricle; (5) the presence of old rheumatic heart disease (almost universal); (6) auricular fibrillation; (7) mitral stenosis (not believed essential); (8) the presence of a murmur which could be established definitely as one of tricuspid insufficiency—or, even better—stenosis. (The present authors suspected tricuspid stenosis, but were never quite sure, and hesitated to make this rare diagnosis.) (9) marked engorgement of the liver, with a systolic pulsation; (10) a series of striking variations of this syndrome from extreme severity to relatively normal conditions, and vice versa, within short periods of time (six to forty-eight hours). This is the most important differential point between the possibility of a loose, riding thrombus and permanent organic changes in the tricuspid valve. Particularly noteworthy was the marked change in the roentgenograms of the heart within twenty-four hours, which occurred Feb. 24 to 25, 1943. It emphasized the importance of making serial roentgenograms during the fluctuating clinical phases whenever this syndrome is suspected.

Studies of particular interest which were not carried out in this case would be serial, carefully controlled, direct venous, and, if possible, direct arterial, pressure studies, and opaque medium studies of the

chambers of the heart. The effect, if any, of slow and sudden changes of posture would have been of interest.

Several pathologic changes are worthy of further comment. In this heart, as in most instances of ball thrombi in the left auricle, the mitral valve showed definite evidence of stenosis. It has been felt that stenosis encourages the formation and retention of ball thrombi. In this case, however, although the thrombus was in the right auricle, there was no evidence of tricuspid stenosis—rather, the tricuspid valve was markedly dilated—although this was considered to be secondary to the pressure of the thrombus in its endeavor to pass through. It was difficult indeed to understand how sufficient blood to maintain life could pass around the enormous ball and through the valve.

The history and the roentgenograms of August, 1942, suggest that this thrombus had probably been present for a period of six months or longer.

Characteristically, auricular fibrillation was present. This favors the development of mural thrombi and probably their detachment. The incomplete emptying and tendency to a rotary motion of the blood no doubt help to keep the thrombus from lodging permanently in the orifice. These same factors tend to develop the spherical shape by molding and grinding the surface as new accretions are added.

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Abstracts and Reviews

Selected Abstracts

Remington, J. W., Cartland, G. F., Drill, V. A., and Swingle, W. W.: Purification and Bioassay of Tissue Extracts Capable of Lowering the Blood Pressure of Hypertensive Rats. Am. J. Physiol. **140:** 627, 1944.

The protein material contained in various hog tissues which will lower the blood pressure of the hypertensive rat has been partially purified by ammonium sulfate and acetone fractionation steps. The evidence seems to suggest that this material is contained solely in the albumin fraction. Horse serum was found to be an exceptionally rich source of the active protein.

A rat assay method for the testing of this active material has been constructed, based on the blood pressure reduction obtained in hypertensive rats after intramuscular injections of the test material over a four day period. It has not been found possible to maintain the blood pressure below the hypertensive level for longer than ten to twenty days, even though extract injections were given continuously.

The reduction in blood pressure does not appear to be due to a general reaction to a foreign protein. Neither, however, can it be attributed to a single chemical entity contained solely in the kidney.

AUTHORS.

Wiggers, H. C., and Middleton, S.: Cardiac Output and Total Peripheral Resistance in Posthemorrhagic Hypotension and Shock. Am. J. Physiol. **140:** 677, 1944.

Utilizing a "modified Stewart Method" for determining cardiac output, variations of the latter and of total peripheral resistance (TPR) were studied during the course of standardized hemorrhagic shock in relation to other cardiodynamic events and hematocrit changes.

During a ninety minute period at 50 mm. Hg hypotension, and a subsequent forty-five minute period at 30 mm Hg, cardiac output and stroke volume were reduced to 29 to 45 per cent of the control flow. Although they were restored to normal in the majority of experiments immediately after reinfusion, in some the recovery was only to 45 to 85 per cent of control values. During the three hours succeeding reinfusion, cardiac output decreased rapidly and was the chief cause of the declining arterial blood pressure. In the final stages, cardiac output stabilized at low levels, and the continued fall of blood pressure was occasioned chiefly by peripheral factors. Slowing and failure of the heart were often the ultimate steps in the series of cardiodynamic events leading to death.

Hematocrit readings indicated a *hemodilution during the periods of hypotension* and a tendency toward concentration following reinfusion of the blood.

The course of events in standardized hemorrhagic shock is, therefore, similar to that described in other experimental types in that (a) hemoconcentration occurs, and (b) progressive reduction of cardiac output is chiefly *responsible for the progressive decline of arterial pressures after reinfusion.*

Despite the universally fatal outcome, changes in the total peripheral resistance were extremely variable during the periods of posthemorrhagic hypotension and during circulatory failure, which developed after reinfusion of blood. The different trends are analyzed. Arguments are advanced that physical factors concerned in such changes can be evaluated, and that an estimate of directional changes in vasomotor tone can be made. Supplementary evidence is cited from which the conclusion is reached that humoral or metabolic factors play a considerable role in these changes.

In the method for producing shock by holding mean arterial pressures at successive levels of 50 and 30 mm. Hg for specified intervals of time, cardiac output was reduced to 29 to 45 per cent of the original blood flow. Such ranges of reduction indicate that the procedure recommended for the rather regular production of hemorrhagic shock does not result in equivalent reductions of circulatory values when applied to different animals. Of course, the possibility that other factors may enter cannot be excluded.

AUTHORS.

Hamilton, W. F., Woodbury, R. A., and Harper, H. T., Jr.: Arterial, Cerebrospinal, and Venous Pressures in Man During Cough and Strain. Am. J. Physiol. **141:** 42, 1944.

Differential pressure records, which separate the changes in arterial pressure which are due to simple propagation of intrathoracic pressure from those which are due to changes in blood flow, are shown. It is shown that increases due to the first of the above causes, strain only the peripheral arteries, whereas increases due to changes in blood flow or to changes in peripheral resistance, strain also the vital arteries to the brain, spinal cord, and viscera.

The nature of the cerebrospinal pressure pulsations is discussed.

During the preliminary pressure rise of the cough, people whose circulation is hypodynamic show arterial pressures which are no higher than simultaneous intrathoracic pressures. During brief intervals there is, therefore, no effective head of pressure to irrigate the coronary or other vital vascular beds.

During the expulsive phase of the cough, the arterial pressure may continue to rise while the intrathoracic pressure is going down, or the arterial pressure may descend more slowly than the intrathoracic pressure. This signifies that the pressure distending the aorta is rising and, since it often occurs during diastole, it implies that during the expulsive phase of a cough blood is forced from the lungs through the relaxed left heart and into the aorta.

The cough may force blood into the aorta in cases with hypodynamic circulation and in cases with congestive heart failure. This may occur in normal individuals but no evidence has been obtained to support the idea that it does.

AUTHORS.

Stead, E. A., Jr., and Warren, J. V.: The Effect of the Injection of Histamine Into the Brachial Artery on the Permeability of the Capillaries of the Forearm and Hand. J. Clin. Investigation **23:** 279, 1944.

Histamine injected intra-arterially increases the permeability of the capillaries supplied by the artery. The rapid loss of protein from the plasma can be detected by comparing the blood draining from the part before and after the injection. The hematocrit reading and hemoglobin concentration increased markedly while the protein concentration rose only slightly.

A reaction similar to that produced by histamine is not seen in uninjured tissue in the usual types of shock.

AUTHORS.

Bailey, C. C., and Betts, R. H.: Cardiac Arrhythmias Following Pneumonectomy. New England J. Med. 229: 356, 1943.

Functional cardiac arrhythmias, especially auricular fibrillation and auricular flutter, occurred in eight of 78 patients who received total pneumonectomy but had no evidence of heart disease. In the authors' opinion, these arrhythmias alone do not indicate heart disease.

It seems best to restore the heart to normal rhythm as soon as practicable, either by rapid digitalization or, in selected cases, by quinidine sulfate, since heart failure may result if an excessively rapid cardiac rate continues over many days.

The etiology of these arrhythmias is unknown. The hypothesis is suggested that the precipitating factor is vagal irritation from a stitch abscess or infection of the bronchial stump, in the presence of hyperexcitability of the auricular muscle resulting from marked displacement of the mediastinum.

AUTHORS.

Currens, J. H., White, P. D., and Churchill, E. D.: Cardiac Arrhythmias Following Thoracic Surgery. New England J. Med. 229: 360, 1943.

Cardiac arrhythmia is occasionally noted following thoracic surgery. Twelve patients are reported from a series of 56 who underwent surgery for carcinoma of the lung or esophagus. Eight had auricular fibrillation, and four auricular flutter.

Age seems to be a predisposing factor, since arrhythmia of the heart seldom occurs following thoracic surgery below the age of 40 years.

Quinidine sulfate may be used to advantage in such patients as a prophylactic measure during the postoperative period.

AUTHORS.

Mayer, C. P., Lepera, L., and Pataro, F. A.: Character of the Precordial Ventricular Complex in ECG Tracings With Deviation of the Electric Axis to the Left. Rev. argent. de cardiol. 10: 223, 1943.

The precordial leads have a definite pattern in cases of left ventricular strain. In other types of left axis deviation, they do not differ from the normal controls. Therefore, the precordial leads are of value in the differential diagnosis between left ventricular strain and other types of left axis deviations. In the latter cases, when the precordial leads differ significantly from the normal, a coronary disease may be suspected.

AUTHORS.

Yuskis, A. S.: Aneurysm of the Right Pulmonary Artery With Rupture Into Bronchus, and a Patent Ductus Arteriosus; Report of a Case. California & West. Med. 58: 272, 1943.

A congenital aneurysm confined to the right branch of the pulmonary artery, with rupture into the bronchus and a patent ductus arteriosus, is reported. An ante-mortem diagnosis, which was confirmed at autopsy, was made by the x-ray department of the State University of Iowa. This case report makes a total of thirty-one cases diagnosed ante mortem, and a total of 144 cases reported to the present time. The patient had relatively few symptoms and signs. There was no elevation of blood pressure, no prominence of the left side of the chest, no right-sided cardiac hypertrophy, and no electrocardiographic changes. The roentgen ray was unquestionably of chief assistance in establishing the diagnosis. The occurrence of these aneurysms is rare, but it is important to emphasize their consideration in the differential diagnosis of hemoptysis.

AUTHOR.

Hurst, A., Bassin, S., and Levine, I.: Miliary Densities Associated With Mitral Stenosis. Am. Rev. Tuberc. 49: 276, 1944.

Chest x-ray surveys for tuberculosis are productive of a great deal of information on nontuberculous conditions.

Several cases of bilateral, symmetrical, diffuse, nodular, pulmonary densities associated with rheumatic mitral stenosis were discovered in draftees.

These miliary densities must be carefully distinguished from similar appearing conditions, such as miliary tuberculosis, sarcoidosis, pneumonoconiosis, carcinomatosis, etc.

An explanation for the varying roentgenographic appearance has been offered in the light of the probable pathologic and physiologic background.

AUTHORS.

Wedum, A. G., and Wedum, B. G.: Rheumatic Infections in Cincinnati Hospitals. Am. J. Dis. Child. 67: 182, 1944.

There was a total of 3,475 admissions of patients with rheumatic infections to all hospitals in Cincinnati for the period from Jan. 1, 1930 to Dec. 31, 1940. Analysis of the records of these admissions and comparison with similar data obtained in Philadelphia for the period from 1930 through 1934 revealed the following facts:

The rheumatic syndrome was more nearly the same in Negroes in the two cities than it was in white persons. Negroes constituted a considerably greater proportion of the patients with rheumatic heart disease with rheumatic fever, and a somewhat smaller proportion of those with chorea than would be expected from their proportion in the population and in patients admitted to hospitals. Chorea is more common in Negroes than is generally realized.

In white persons in Cincinnati the incidence of rheumatic fever was lower, and the acute manifestations were less frequent, than in Philadelphia, and both morbidity and case mortality among children were lower. Among adults above the age of 35 years, the annual incidence of rheumatic heart disease per hundred thousand of population was greater in Cincinnati; this group accounted for more of the patients who died in Cincinnati than in Philadelphia. Adequate convalescent care for white children, and comparatively inadequate length of hospitalization for adults in Cincinnati, provide a possible explanation for these differences.

The data accumulated in this survey tend to corroborate the growing conviction that convalescent care, of proved value for children with rheumatic fever, should be given also to young adults. This concept is of major importance in handling rheumatic infections among young persons in military service.

AUTHORS.

Kuttner, A. G., and Krumwiede, E.: Observations on the Epidemiology of Streptococcal Pharyngitis and the Relation of Streptococcal Carriers to the Occurrence of Outbreaks. J. Clin. Investigation 23: 139, 1944.

Major and minor outbreaks as well as sporadic cases of streptococcal pharyngitis occurring in groups of rheumatic children in a sanatorium during a six-year period are described.

Major outbreaks were due to Group A *streptococci* of a single type not previously present, and were not preceded by a rise in carrier rate.

Minor outbreaks were preceded by a slow spread from carriers to other individuals without at first causing infection. Subsequently, a small number of clinical cases due to these types developed.

Sporadic cases arose directly from carriers and were not preceded by a dissemination of the streptococci to healthy individuals.

The length of the carrier state was studied.

Twenty-nine per cent of the children admitted during the summer and fall months were carriers of Group A hemolytic streptococci. With few exceptions, these microorganisms did not spread to other individuals and disappeared after a few months.

The epidemic-inducing types of streptococci persisted longer in "post-infection" than in "contact" carriers.

The length of the carrier state was not related to the presence or absence of tonsils.

AUTHORS.

Kuttner, A. G., and Lenert, T. F.: The Occurrence of Bacteriostatic Properties in the Blood of Patients After Recovery From Streptococcal Pharyngitis. J. Clin. Investigation 23: 151, 1944.

The development of bacteriostatic properties in the blood of children, after recovery from upper respiratory infections due to Group A streptococci of a single type, is reported.

AUTHORS.

Higgins, G. K.: The Effect of Pulmonary Tuberculosis Upon the Weight of the Heart. Am. Rev. Tuberc. 49: 255, 1944.

The total heart weights of 600 carefully selected patients dying from pulmonary tuberculosis have been tabulated by age, body length, and estimated body weight. These have been compared with normal heart weights selected from the literature.

Right ventricular weights above Müller's averages were found in 23 per cent of the tuberculous patients and a ventricular ratio (L/R) of less than 1.3 was present in 40 per cent. The right ventricle weighed more than the corresponding left in 15 per cent of the tuberculous patients.

It was not possible to determine a definite relationship between right ventricular hypertrophy and pleural adhesions, pulmonary collapse, or the type and extent of the pulmonary tuberculosis.

A definite relationship existed between right ventricular hypertrophy and the clinical duration of the disease.

Left ventricular hypertrophy was not noted in this series.

A theory has been presented to explain the presence of right ventricular hypertrophy in some patients and its absence in others with similar tuberculous lesions.

AUTHOR.

Gordan, G., Soley, M. H., and Chamberlain, F. L.: Electrocardiographic Features Associated With Hyperthyroidism. Arch. Int. Med. 73: 148, 1944.

In this series of cases of hyperthyroidism the noteworthy electrocardiographic findings in order of frequency were: (1) sinus tachycardia, (2) various abnormalities of the T waves, of which low amplitude and notching were the most common, (3) auricular fibrillation, (4) partial auriculoventricular block, and (5) in rare instances, auricular flutter. After exclusion of other causes for electrocardiographic abnormalities, the incidence of these findings was the same for the younger (14 to 40 years of age) and for the older (41 to 75 years of age) groups of patients. After treatment of hyperthyroidism, the abnormalities tend to disappear. In the presence of hyperthyroidism, electrocardiograms must be interpreted with caution, since they may simulate those of persons with organic heart disease.

AUTHORS.

Middleton, S., and Wiggers, C. J.: The Effects of Renin and Angiotonin on Cardiac Output and Total Peripheral Resistance. Am. J. Physiol. **141:** 128, 1944.

The effect of renin and angiotonin on cardiac output was studied by a refined quantitative cardiometer method.

Small doses cause insignificant changes in systolic discharge in the direction of slight increases or decreases, but the concomitant slowing reduces cardiac output per minute slightly. A study of changes in total peripheral resistance indicates that the pressor rise offers a reasonable indication of the magnitude of peripheral vasoconstriction.

More potent doses, generally those which cause a pressor effect of 30 mm. Hg or more, result in a variable reduction in systolic discharge and, together with cardiac slowing, may reduce cardiac output per minute very significantly. In such instances, pressor effects underestimate the change in total peripheral resistance considerably.

Since such cardiac depression may persist after use of larger doses, the return of arterial pressure to control levels may not be a sign that its peripheral action has passed off. In all tests requiring repeated injections, it is recommended that doses be used which do not evoke pressor effects in excess of 30 mm. Hg.

AUTHORS.

Middleton, S.: The Effects of Renin and Angiotonin During Hemorrhagic Hypotension and Shock. Am. J. Physiol. **141:** 132, 1944.

The effects of renin and angiotonin in doses causing a pressor response of 30 mm. Hg, or less, were determined during two stages of posthemorrhagic hypotension and at various periods after reinfusion of the blood, i.e., during development of precipitate or delayed circulatory failure regarded as characteristic of shock.

In confirmation of other investigators, it was found that the pressor responses to *both* of these agents diminished and then disappeared during the prolonged hypotension, but recovered and increased progressively after reinfusion of the blood, despite the development of circulatory failure.

The results failed to support the suggestion that the mechanisms by which renin is activated are implicated in the development of circulatory failure, and that the gradual return of response during progressive circulatory failure after reinfusion remains unexplained.

AUTHOR.

Jonnard, R., and Thompson, M. R.: The Nature of the Pressor and Depressor Factors Derived From the Kidney. J. Am. Pharm. A. 32: 260, 1943.

Various hypotensive kidney extracts have been fractionated and the acute effects upon the carotid and femoral arterial blood pressure, pulse rate, abdominal vasomotor system, respiration, and electrocardiogram have been studied in anesthetized and nonanesthetized dogs and cats. The substance or substances which are responsible for the production of prolonged hypotension in normal animals are characterized by their solubility in water, strong alcohol, concentrated acetone, dichloroethylene, by the presence of phenolic hydroxyls of a tryptophan group, by the absence of free histidine, or reducing properties, or sterols, lipids, and phospholipids groups, by their destructive oxidation by vegetable phenolase, by their slow mobility in the electrophoretic field, by their isoelectric point between pH 5.0 and 7.0, and by their incapacity to traverse ultrafilters. These facts indicate the presence of complex molecules which are responsible for the slow resorption rate. This, in turn, explains the prolonged hypotension produced when these substances are injected sub-

cutaneously or intramuscularly. The pharmacologic properties of the kidney hypotensive extracts described and their effects upon the arterial blood pressure and the action current of the heart are apparently not specific of the substances considered when compared with records obtained in human cases of essential hypertension. The destructive oxidation of renin and of the hypotensive kidney extracts by vegetable phenolase (tyrosinase) has been studied. It has been demonstrated that, while renin yields upon oxidation an unstable strongly hypotensive substance, the oxidation of the hypotensive kidney extracts yields an inactive preparation, and that the two reactions proceed independently in mixtures containing both factors, so that there is no in vitro chemical antagonism or reciprocal neutralization between renin and the kidney hypotensive fractions isolated. The possible role of these substances and of renin in the pathogenesis of hypertension of renal origin has been discussed in the light of a number of clinical facts reported to date. It is advanced that possibly the role of the kidney derangement is more of a metabolic nature than of a humoral one. On the other hand, results of the oxidation experiments reported suggest a new therapeutic approach worth further investigation.

JONNARD.

Greenfield, I.: Thrombosis and Embolism of the Abdominal Aorta. Ann. Int. Med. **19:** 656, 1943.

A case of embolism of the abdominal aorta is reported.

The association of miliary tuberculosis, peritonitis, urinary sepsis, and yellow atrophy of the liver with thrombosis of the abdominal aorta was noted.

Variations from the classical clinical syndrome of occlusion of the abdominal aorta were cited.

Five additional cases of occlusion of the abdominal aorta were added, making the total number of cases now on record 161.

AUTHOR.

Watson, J. R., Lichty, J. M., Hill, J. M., and Miller, R. B.: The Use of Venograms for the Localization and Study of Arteriovenous Fistula. Surg., Gynec. & Obst. **76:** 659, 1943.

Three cases of arteriovenous fistula of the common femoral vessels are reported in which venography was proved to be a reliable means of locating the level of the fistula.

Studies of the venograms in each instance showed the vein distal to the fistula to be normal.

The venograms demonstrated a marked difference in the collateral venous circulation between one case in which the vein had been ligated distal to the fistula at the time of injury for control of hemorrhage, and two cases in which this had not been necessary.

Ligation of the vein distal to the fistula appears to have the same beneficial effect on the extremity that ligation proximal to the fistula has on the heart.

AUTHORS.

Reich, N. E.: Occlusions of the Abdominal Aorta: A Study of 16 Cases of Saddle Embolus and Thrombosis. Ann. Int. Med. **19:** 36, 1943.

Occlusion of the abdominal aorta should be strongly suspected when there is a sudden onset of pain of varying intensity in the lower extremities and pelvis with temperature and color changes, sensory disturbances, and weakness or paralysis. This possibility becomes greater when occurring in females with auricular fibrillation due to rheumatic heart disease, especially when signs of embolization have occurred in other organs. An early diagnosis may result in cure or arrest by surgical

intervention (embolectomy), heparinization, or other appropriate medical measures described herein.

AUTHOR.

Doane, J. C.: Embolism and Thrombosis of the Popliteal Artery—Diagnosis and Treatment. Ann. Int. Med. 19: 634, 1943.

Eleven cases of popliteal occlusion were presented. Comments on the symptoms as related to diagnosis were made. The necessity of early diagnosis was stressed, it being stated that treatment, whether it be radical or conservative, must be begun within the first six hours if good results are to be expected.

The value of a carefully planned conservative routine was pointed out. The technique of heparinization was briefly described.

AUTHOR.

Chamberlain, E. N.: Bacterial Aneurysm. Brit. Heart J. 5: 121, 1943.

Three new cases of bacterial aneurysm are described: one of the femoral artery, one probably of the radial artery, and one of the mesenteric artery. The last ruptured, causing death from hemorrhage into the peritoneal sac. The post mortem findings are recorded in two cases.

Nineteen other cases have been collected, reported since 1923 when the subject was fully dealt with by Stengel and Wolferth. These have been analyzed.

AUTHOR.

Hamilton, W. F.: The Patterns of the Arterial Pressure Pulse. Am. J. Physiol. 141: 235, 1944.

The pressure pulse patterns in various arteries are described in terms of the filling and emptying of the arterial tree and the added reflected waves which are contributed by the various arteries. It is shown that these waves are reflected from constricted arterioles, and that the form of the pulse may be used to evaluate the role of vasodilation in producing hypotension.

AUTHOR.

Warren, J. V., and Stead, E. A., Jr.: Fluid Dynamics in Chronic Congestive Heart Failure: An Interpretation of the Mechanisms Producing the Edema, Increased Plasma Volume and Elevated Venous Pressure in Certain Patients With Prolonged Congestive Failure. Arch. Int. Med. 73: 138, 1944.

Edema develops in chronic congestive failure because the kidneys do not excrete salt and water in a normal manner. This disturbance in renal function is related to the decreased cardiac output, and not to engorgement of the kidneys from an increased venous pressure, because the salt and water retention may occur before there is a rise in venous pressure.

The increase in the plasma volume is a manifestation of the retention of salt and water. The resulting decrease in concentration of the plasma proteins usually stimulates production of plasma protein so that the total amount of circulating protein increases. The plasma volume is thus increased in size without a marked lowering of the osmotic pressure of the plasma proteins.

In due time, the increase in the blood volume and the extracellular fluid volume causes a rise in the venous pressure. The osmotic pressure of the plasma proteins and the increased pressure of the extracellular fluid provide the physical forces which enable the large plasma volume to be maintained in the presence of the high capillary pressure which results from the high venous pressure.

Local differences in venous pressure are of importance in that they determine the placement of the salt and water which are retained by the kidneys in congestive heart failure.

Other factors than retention of salt by the kidneys account for the rise in venous pressure in acute heart failure. In many patients the rise in venous pressure represents the summation of the effects of acute and chronic heart failure.

AUTHORS.

Rinzler, S. H., Travell, J., and Civin, H.: The Oscillometric Index: An Aid in Evaluating the Arterial Status of the Lower Extremities. Arch. Int. Med. 73: 241, 1944.

The oscillometric index (ratio of the oscillometric reading at the ankle to that at the wrist), the cutaneous temperature following posterior tibial nerve block, and the presence or absence of calcification of the vessels of the lower extremities in the roentgenogram were determined for eighty-four ambulatory patients with heart disease.

A correlation of the data obtained by these three laboratory aids (oscillometry, cutaneous temperature test, and soft tissue roentgenogram) shows that, as the oscillometric index decreases, the incidence and extent of calcification of the vessels of the lower extremity, and the incidence of abnormal cutaneous temperatures increase.

In the presence of a normal circulation in the upper extremity, an oscillometric index of 0.75 or more almost always indicates adequate arterial function in the lower extremity. Similarly, an index of less than 0.75 indicates sclerotic changes in the arteries of the leg, probably with calcification, and an index of 0.3 or less indicates extensive calcification and probably advanced occlusive arterial disease.

The oscillometric index is of greater value in estimating the presence and degree of arteriosclerotic disease in the lower extremity than is the oscillometric reading at the foot or ankle when the latter readings fall within an intermediate range of about 1 to 4 at the ankle and ⅛ to 2 at the foot.

An oscillometric reading of 4 at the ankle or more than 2 at the foot nearly always indicates normal arterial flow, and a reading of less than 1 at the ankle or 0 at the foot indicates occlusive arterial disease.

Roentgen examination for calcification of the vessels usually affords the earliest evidence of arteriosclerosis of the lower extremities.

Final appraisal as to the degree of occlusive arterial disease of the lower extremities ideally should be based on examinations which include determination of both the oscillometric index and the vasodilatation temperature.

Duplicate determinations of cutaneous temperature on ten patients showed that a variation of several degrees (C.) in the room temperature does not materially influence the vasodilatation temperature after posterior tibial nerve block.

AUTHORS.

Kohlstaedt, K. G., and Page, I. H.: Hemorrhagic Hypotension and Its Treatment by Intra-Arterial and Intravenous Infusion of Blood. Arch. Surg. 47: 178, 1943.

A method for producing hemorrhagic shock is described which produces severe sustained hypotension without increase of bacterial contamination or the use of excessive amounts of anticoagulants. Spontaneous recovery does not occur. An apparatus is described for return of the blood removed through an artery under controlled pressure.

The severity of the effects of the hypotension on the vascular system was ascertained by the pressor response to angiotonin or epinephrine. If the response is not restored after treatment the chance of survival is poor, but the return of responsiveness does not insure survival.

When all the blood removed is returned by the intra-arterial route under a pressure of 50 mm. of mercury the systemic arterial pressure rises rapidly and recovery

occurs. The same amount of blood given intravenously usually causes recovery, but not quite so certainly as blood given into an artery.

Readministration of only 50 per cent of the blood by vein resulted in recovery of 30 per cent of the dogs, while the same amount given intra-arterially resulted in recovery of 75 per cent.

When blood is given intra-arterially to animals with severe hypotension two precautions should be observed: First, the pressure should not be greater than 50 mm. of mercury, and it should be elevated stepwise. Second, the rate of administration of the fusion should be guided by the venous pressure.

Intra-arterial infusions have been given three patients in severe shock to demonstrate the practicality of the procedure.

It is suggested that the method may have value when the amount of plasma or blood available is insufficient or when the arterial pressure is excessively low.

AUTHORS.

Rich, Arnold R.: A Peculiar Type of Adrenal Cortical Damage Associated With Acute Infections, and Its Possible Relation to Circulatory Collapse. Bull. Johns Hopkins Hosp. 74: 1, 1944.

Various acute infections produce damage to the adrenal cortex, leading to necrosis of isolated cells, and to a striking transformation of the solid cords of the zona fasciculata into tubular structures containing an inflammatory exudate.

The possible relation of this adrenal cortical damage to the circulatory collapse that occurs in some of the patients who suffer from these infections, is suggested.

AUTHOR.

Cole, W. H., Allison, J. B., Murray, T. J., Boyden, A. A., Anderson, J. A., and Leathem, J. H.: Composition of the Blood of Rabbits in Gravity Shock. Am. J. Physiol. **141**: 165, 1944.

Rabbits suspended head up, without anesthesia, became unconscious in from twenty to one hundred and twenty minutes, even though breathing continued at a rate about one half that of normal. Thirty per cent of the animals died within twenty-four hours although all external symptoms appeared normal.

Other changes resulting from suspension were: (a) marked reduction of blood pressure, (b) suppression of urine flow, (c) metabolic acidosis (pH = 7), (d) decreased blood carbon dioxide and venous oxygen, (e) increased plasma lactate, phosphate, pyruvate, potassium, and nonprotein nitrogen, (f) increased or decreased plasma glucose, and (g) decreased plasma chloride in well-fed animals.

There were no constant or significant changes in hematocrit, plasma specific gravity, protein, sodium, or calcium, or in the blood cell counts.

Hemoconcentration did not occur.

Suspension resulted in a peripheral circulatory deficiency leading to tissue hypoxia. Altered concentrations of certain blood metabolites occurred, which were useful in determining the severity of shock, and the course of recovery, when the rabbits were returned to the horizontal position.

AUTHORS.

Houchin, O. B., and Smith, P. W.: Cardiac Insufficiency in the Vitamin E Deficient Rabbit. *Am. J. Physiol.* **141**: 242, 1944.

We have shown that rabbits in a state of nutritional muscular dystrophy as the result of Vitamin E deprivation exhibit the following signs of severe myocardial damage:

A greatly increased sensitivity to posterior pituitary extracts; they are killed by doses much smaller than those which are well tolerated by normal control animals.

A high resistance to the toxic effects of the cardiac glycosides; their lives are preserved for several days beyond the predicted time of death in the majority of cases, by doses of digoxin or ouabain which are lethal to normals.

Probable cardiac dilatation, as revealed by thoracic x-ray films.

From these findings we conclude that the sudden death of Vitamin E deficient animals in an advanced stage of muscular dystrophy is due directly to myocardial failure.

AUTHORS.

Mayerson, H. S.: Orthostatic Circulatory Failure ("Gravity Shock") in the Dog. Am. J. Physiol. 141: 277, 1944.

Anesthetized dogs, suspended in the upright (feet down) position for twenty minutes to four hours, show varying degrees of hypotension, progressive hemoconcentration, and marked increases in arterio-venous oxygen and carbon dioxide differences. After ten to twenty minutes, the plasma protein level diminishes, while the protein concentration of lymph increases. These changes can be reversed by returning the animals to the horizontal position and approximately controlled values are achieved in about thirty minutes.

Animals kept in the upright position are extremely sensitive to hemorrhage. Irreversible failure is often precipitated by the withdrawal of relatively small quantities of blood (30 to 50 c.c.). This can usually be prevented, and the response of tilting improved, by the infusion of saline and/or blood during the upright period.

AUTHOR.

Stead, E. A., Jr., and Warren, J. V.: The Protein Content of the Extracellular Fluid in Normal Subjects After Venous Congestion and in Patients With Cardiac Failure, Anoxemia, and Fever. J. Clin. Investigation 23: 283, 1944.

The filtrate from the capillaries of the skin and subcutaneous tissues normally contains some protein. On the average, it does not contain more than 0.24 gram per cent of protein. It probably contains much less.

Elevation of the venous pressure in the leg to a level equal to 30 mm. Hg. produces edema which contains from 0.4 to 1.3 grams per cent of protein, with an average of 0.8 grams per cent.

Cardiac failure does not make the capillaries of the leg more permeable to protein.

Generalized anoxemia, sufficient to cause impaired cerebral function, does not cause increased permeability of capillaries in the leg. Although local ischemia produces capillary damage and leakage of protein, generalized stagnant anoxia, of a degree compatible with life, does not make the capillaries of the leg more permeable to protein.

Fever and acute infectious disease cause no abnormal increase in permeability to protein in the capillaries of the leg.

AUTHORS.

Wilburne, M., and Ceccolini, E. M.: Heart Disease in Selective Service Examinees. A Study of 20,000 Examinees in the Pacific Northwest. Am. J. M. Sc. 207: 204, 1944.

A study of 20,000 consecutive Selective Service examinees, representing a cross-section of male population 20 to 45 years of age in the Pacific Northwest, revealed the existence of heart disease in 288 men, an incidence of 1.44 per cent. This figure constituted 6 per cent of rejections of all physical and mental defects.

Rheumatic heart disease was observed in 183 examinees, or 63.5 per cent of cardiac rejections and 9.15 men per 1,000 examined. Congenital heart disease

followed in frequency, occurring in 35 men (12.2 per cent of rejections for heart disease, or 1.75 men per 1,000 examined). There were nine instances of arteriosclerotic heart disease, six examinees with hypertensive heart disease, three cases each of hyperthyroid heart disease and effort syndrome (neurocirculatory asthenia), two instances of paroxysmal tachycardia, and one case of chronic constrictive pericarditis.

There were 46 cases of organic heart disease of unknown etiology, or 16 per cent of total cardiac rejections and 2.3 men per 1,000 examined.

In the 183 examinees rejected for rheumatic heart disease the mitral valve was involved alone in 152 cases (3.1 per cent), the aortic valve was involved alone in eight examinees (4.4 per cent), and combined mitral and aortic valve defects were observed in 23 cases (12.5 per cent).

Functional murmurs were noted in 297 examinees, an incidence of 1.48 per cent of the total number of men examined. This figure represents an incidence slightly higher than that observed for all forms of cardiac disease combined.

The figure of 288 men rejected for heart disease (1.44 per cent of 20,000 examinees) is of interest in comparison with 4,820 rejected for all physical and mental defects (24.1 per cent of examinees).

AUTHORS.

Plentl, A. A., and Page, I. H.: The Action of Crystalline Proteolytic Enzymes on Angiotonin. J. Exper. Med. **79:** 205, 1944.

Angiotonin was subjected to enzymatic digestion by crystalline carboxypeptidase, chymotrypsin, trypsin, and pepsin. These enzymes were found to destroy it in vitro. Hydrogen ion optima and proteolytic coefficients for these reactions were determined and were found to be of approximately the expected magnitude for typical substrates.

Regarding the purified crystalline enzymes as reagents, the experimental findings were interpreted on the basis of Bergmann's specificity studies. The authors were thus directed to the conclusion that angiotonin contains (1) a free terminal amino group, (2) a free terminal carboxyl group, (3) one basic amino acid residue which may be terminal but its carboxyl must be united in a peptide linkage, (4) one central dibasic amino acid residue in combination with an aromatic amino acid residue, (5) an aromatic amino acid residue which may be part of (4) and, if not part of (4) must be terminal with its carboxyl group in peptide linkage. The simplest compound satisfying these conditions is tyrosyl-arginyl-glutamyl-phenylalanine or a combination of amino acids with similar general characteristics.

AUTHORS.

Koffler, A., and Freireich, A. W.: Thrombophlebitis as a Hitherto Unreported Complication of Thiocyanate Therapy of Hypertension. Am. J. M. Sc. **207:** 374, 1944.

Four cases of thrombophlebitis (an incidence of 10 per cent) are reported as occurring in the course of therapy of hypertension with thiocyanate. This high frequency is much greater than can be explained on pure coincidence, and must be accepted as a toxic effect which has not been previously reported.

It does not appear to be related to the level of thiocyanate in the blood, and may occur early or late in the course of treatment.

AUTHORS.

Book Reviews

ESTUDO PATOLÓGICO DA AÇÃO DO TABACO DESNICOTINIZADO SÔBRE OS VASOS SANGUÍNEOS DO RATO BRANCO: By J. Lopes de Faria, Universidade de Minas Gerais. Grafica Queizoz Breiner Ltda., Belo Horizonte, Brazil, 1943, 107 pages, 56 illustrations.

Forty-one rats were injected with a denicotinized extract of tobacco which was prepared according to Harkavy's technique. Thirteen rats served as controls, and were injected with saline solution. In the latter parts of the experiments, which lasted 114 days, doses of 4 times as much and then 18 times as much of the extract as Harkavy used were injected. Chronic endocarditis, myocarditis, and pericarditis were noted on microscopic examination of both test animals and control animals. The author concludes that nicotine-free extracts of tobacco, specifically that grown in Minas Gerais, do not produce pathologic changes in the blood vessels of the hearts and extremities of white rats. He was thus unable to confirm the studies of Harkavy. This, he believes, may be due to the fact that the tobacco which he used had a lower "antigen power" than that employed by Harkavy.

EDGAR V. ALLEN.

SINDROME CORONARIO LATERAL: By Guillermo A. Bosco, Professor Titular de Semiologia y Clinica Propedeutica de la Facultad de Ciencias Médicas de Buenos Aires. Imprenta Ferrari Hnos., Buenos Aires, 1943, 168 pages, 83 illustrations.

As is made clear in the introduction, this monographic study strives to establish the "lateral coronary syndrome" as an anatomicoclinical entity to be considered together with the "anterior" and "posterior" coronary syndromes.

The syndrome is caused by occlusion of the left circumflex artery in its terminal portion. This artery is distributed over the lateral portion of the left ventricle in about 80 per cent of all persons, and over the posterior part of the septum and the right ventricle in the others. The author states that this possibly "anomalous" distribution need not be taken into account, for only the left ventricle might show the effects of acute ischemia; it is the reviewer's opinion that this is not valid.

The first part of the book is devoted to an anatomic and pathologic study, and is illustrated by exceptionally clear photographs. A physiopathologic study follows.

The clinical signs of the "lateral syndrome" are discussed in detail. In spite of the author's efforts, they do not seem to be essentially different from those caused by occlusion of other coronary arteries. The cardiac manifestations are sinus tachycardia, gallop rhythm, friction rub, functional mitral systolic murmur, and ventricular alternation. It is emphasized that attacks of either left ventricular premature beats or left ventricular tachycardia may occur.

The early electrocardiographic abnormalities are depression of the S-T segment in Leads I and IVF and elevation of the S-T segment in Lead III. Differentiation from posterior infarction may be difficult at times. The author agrees with Wood

and his co-workers, but not with Katz, who describes changes in the S-T segment in Leads I and III similar to those associated with posterior infarction, and changes in the precordial leads like those which occur with anterior infarction, i.e., a special electrocardiographic pattern.

No mention is made of the original description of the syndrome by Wood, Wolferth, and Bellet (AM. HEART J., 16: 387, 1938), nor is there any historical approach or quotation from the literature.

In spite of the efforts of the author, a differentiation between this and other coronary syndromes does not always seem possible.

Wood and his co-workers emphasized the frequency of auricular fibrillation, but Bosco, on the other hand, stresses ventricular premature beats and ventricular tachycardia. This difference of opinion undoubtedly leaves a field for future investigation.

ALDO LUISADA.

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The American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The American Heart Journal is under the editorial supervision of the Association.

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The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

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*Executive Committee.

AMERICAN HEART JOURNAL

For the Study of the CIRCULATION

PUBLISHED MONTHLY
Under the Editorial Direction of
THE AMERICAN HEART ASSOCIATION

VOLUME 27
JANUARY—JUNE, 1944

ST. LOUIS
THE C. V. MOSBY COMPANY
1944

Printed in the
United States of America

Press of
The C. V. Mosby Company
St. Louis

INDEX TO VOLUME 27

An asterisk (*) after a page number indicates the reference is an abstract and not an original article.

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